Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.

SUPPLEMENTARY APPENDIX I

[Protocol Summary]

for

Boceprevir with Peginterferon and Ribavirin

For Chronic Hepatitis C

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PROTOCOL HISTORY

The original P05216 protocol (SPRINT-2) was finalized on 22 MAY 2008. Two general amendments and three site-specific amendments to the original protocol were issued:

- Amendment #1 finalized on 26 MAY 2009
  - Amended language re: contraception and pregnancy testing, laboratory exclusion criteria, scoring of hepatic fibrosis, recommendations for use of hematopoietic growth factors, and drug storage/dispensing

- Amendment #2 finalized on 02 DEC 2009
  - Specified secondary efficacy analyses for the mITT population (subjects who received at least 1 dose of boceprevir or corresponding placebo)
  - Also addressed timing of blood sampling for pharmacogenomic studies

- Site-specific amendments finalized on 20 JUN 2008; 23 OCT 2009 (Germany); and 11 JAN 2010

PROTOCOL SYNOPSIS

Title of Study:	A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1 (Protocol No. P05216)	
Study Sites:	Approximately 200	
Duration of Study:	Approximately 24 months	**Clinical Phase:** 3

Objectives:

Primary Objective: The primary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg three times a day (TID) orally (PO) (hereafter called boceprevir) in combination with PegIntron 1.5 μg/kg weekly (QW) subcutaneously (SC) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO (hereafter called PEG + RBV [WBD]) to therapy with PEG + RBV (WBD) alone in previously untreated adult subjects with chronic hepatitis C (CHC) genotype 1.

Key Secondary Objective: The key secondary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PEG + RBV (WBD) with the standard of care (PEG + RBV [WBD] alone) in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

***Secondary Objectives*:** The secondary objectives of this study are:

- To evaluate the safety of boceprevir when used in combination with PEG + RBV (WBD).
- To define predictors of sustained virologic response (SVR), such as epidemiologic factors, disease characteristics, and on-treatment response.
- To develop the relationship between steady-state pharmacokinetic parameters, obtained from population-based pharmacokinetic model and responses in a subset of subjects.

Methodology: This is a randomized, multi-center study double-blinded for boceprevir or placebo in combination with open-label PEG + RBV (WBD) in previously untreated subjects with CHC genotype 1, to be conducted in conformance with Good Clinical Practice (GCP). This trial consists of three arms: a control arm (Arm 1; PEG + RBV for 48 weeks) and two experimental arms (Arms 2 and 3).

Type of Blinding: Double-blinded (boceprevir).

Sample Size (Including Ratio of Subjects Assigned to Treatments)/Power: This study is projected to enroll a total of 930 non-black/African American subjects (310:310:310) in Arms 1, 2, and 3, respectively. Additionally, a minimum of 150 black/African American subjects will be enrolled with no upper limit for enrollment. Enrollment for the study will close when 930 non-black/African American subjects are randomized and at least 150 black/African American subjects have been randomized.

For statistical comparisons, a step down approach will be taken, where the 48 week experimental group (Arm 3) will be compared against the control arm, and if that test is significant ($p<0.05$), the 28/48 week experimental group (Arm 2) will be compared against the control arm. All the primary efficacy analyses will be based on the data from the 930 non-black/African American subjects. With 310 subjects per arm, the study will have 90% power to detect a combined 13% improvement in the SVR rate, assuming a control SVR rate of 45% (ie, 58% vs 45%) using a 2-sided chi-square test at alpha = 0.05.

With 50 subjects per arm, the true response rate in the black/African American population can be estimated within ± 14% assuming an estimated response rate of 50% and using a 2-sided 95% confidence interval.

Subject Replacement Strategy: No subjects will be replaced.

Randomization: Subjects will be randomized in the three treatment arms in a 1:1:1 ratio. Randomization will be based on a computer-generated random code schedule provided by the sponsor's Biostatistics Department to the interactive voice response system (IVRS).

Stratification: HCV genotype 1a versus 1b, and baseline viral load, ie, high viral load (>400,000 IU/mL) versus low viral load (≤ 400,000 IU/mL) based upon Screening Visit HCV-RNA result.

Diagnosis and Criteria for Inclusion: Adult subjects with CHC HCV genotype 1 and with no previous treatment for CHC will be selected for the study.

The subject must meet ALL criteria listed below for entry:

Inclusion Criteria for CHC:

1. Subject must have previously documented CHC genotype 1 infection. Subjects with other or mixed genotypes are not eligible. The HCV-RNA result obtained from the central laboratory at the Screening Visit must confirm genotype 1 infection and be ≥10,000 IU/mL.
2. Subject must have a liver biopsy with histology consistent with CHC and no other etiology. Copies of the

pathology report and histology slides (suitable for evaluation by the study central pathologist) are required for the subject to be included in the study. The slides and the pathology report must be available at the study site prior to subject randomization. Using the Scoring Systems for Hepatic Fibrosis, the investigator must determine the level of fibrosis demonstrated by the biopsy.

Two unstained slides are preferred for reading by central pathologist selected by the sponsor; however, one slide stained with hematoxylin plus eosin (H & E) plus one slide stained with Masson's trichrome will be accepted (slides should be reviewed by the investigator to confirm adequacy). The central pathologist reading will be used for analysis purposes only; randomization will be performed based upon the local report.

a. No cirrhosis: Biopsy must be within 3 years of the Screening Visit. For biopsies performed more than 18 months prior to the Screening Visit, fibrosis marker testing will be performed to assess level of fibrosis.
b. Cirrhosis: Any historic liver biopsy demonstrating cirrhosis will be sufficient regardless of length of time since biopsy.
c. Subjects whose timing of liver biopsy does not meet the criteria for subject eligibility may have a liver biopsy performed between Screening Visit and Day 1 after the Screening evaluation confirms that the subject meets the study inclusion criteria.

3. Subjects with bridging fibrosis or cirrhosis must have an ultrasound within 6 months of the Screening Visit (or between Screening and Day 1) with no findings suspicious for hepatocellular carcinoma (HCC).

General Inclusion Criteria:

4. Subject must be ≥18 years of age.
5. Subject must weigh between 40 kg and 125 kg.
6. Subject and subject's partner(s) must each agree to use acceptable methods of contraception for at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug, or longer if dictated by local regulations.
7. Subjects must be willing to give written informed consent.

Exclusion Criteria: The subject will be excluded from entry if ANY of the criteria listed below are met:

Clinical Exclusion Criteria:

1. Subjects known to be coinfected with the human immunodeficiency virus (HIV) or hepatitis B virus (HBsAg positive).
2. Subjects who received prior treatment for hepatitis C; other than herbal remedies, except those with known hepatotoxicity (which are exclusionary). All herbal remedies used for hepatitis C treatment must be discontinued before Day 1. Only silymarin (milk thistle) is allowed during the study.
3. Treatment with any investigational drug within 30 days of the randomization visit in this study.
4. Participation in any other clinical trial within 30 days of randomization or intention to participate in another clinical trial during participation in this study. Collection of additional blood, urine, or tissue samples or additional data, beyond that specified in this protocol, is prohibited (other than that related to subject's medical care).
5. Evidence of decompensated liver disease including, but not limited to, a history or presence of clinical ascites, bleeding varices, or hepatic encephalopathy.
6. Diabetic and/or hypertensive subjects with clinically significant ocular examination findings: retinopathy, cotton wool spots, optic nerve disorder, retinal hemorrhage, or any other clinically significant abnormality.
7. Pre-existing psychiatric condition(s), including but not limited to:
   a. Current moderate or severe depression
   b. History of depression associated with any of the following:
      i. Hospitalization for depression
      ii. Electroconvulsive therapy for depression
      iii. Depression that resulted in a prolonged absence from work and/or significant disruption of daily functions
   c. Suicidal or homicidal ideation and/or attempt
   d. History of severe psychiatric disorders (including but not limited to schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder or mania)
   e. Past history or current use of lithium
   f. Past history or current use of antipsychotic drugs for those conditions listed in Exclusion Criterion No. 7d.

8. Clinical diagnosis of substance abuse of the following drugs within the following timeframes (not including time spent in detoxification, hospitalization, or incarceration):
   a. Alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over-the-counter drugs: within 1 year of the Screening Visit OR
   b. Multi-drug abuse (2 or more of the substances listed in Exclusion Criterion No. 8a): within 3 years of Screening Visit OR
   c. Subjects receiving opiate agonist substitution therapy within 1 year of Screening Visit (except for those subjects monitored in an opioid substitution maintenance program OR
   d. Subject's historic marijuana use is deemed excessive by a physician investigator, or is interfering with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must be instructed to discontinue any current use of recreational marijuana prior to entry into study and throughout the study period.
9. Any known pre-existing medical condition that could interfere with the subject's participation in and completion of the study including but not limited to:
   a. Central nervous system (CNS) trauma requiring intubation, intracranial pressure monitoring, brain meningeal or skull surgery, or resulting in seizure, coma, permanent neurologic deficits, abnormal brain imaging, or cerebral spinal fluid (CSF) leak. Prior brain hemorrhage and/or intracranial aneurysms (whether adequately repaired or not)
   b. Current or history of seizure disorder unless seizure was >10 years ago, a single isolated event, no anti-seizure medications prescribed, and a normal neurological examination is documented in study files within 6 months of Day 1
   c. History of stroke or transient ischemic attack
   d. Immunologically-mediated disease (eg, inflammatory bowel disease [Crohn's disease, ulcerative colitis], celiac disease, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, sarcoidosis, severe psoriasis requiring oral or injected treatment, or symptomatic thyroid disorder)
   e. Chronic pulmonary disease (eg, clinical chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, sarcoidosis)
   f. Current or history of any clinically significant cardiac abnormalities/dysfunction (eg, angina, congestive heart failure, myocardial infarction, pulmonary hypertension, complex congenital heart disease, cardiomyopathy, significant arrhythmia) including current uncontrolled hypertension, or history of use of antianginal agents for cardiac conditions
   g. Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the study
   h. Active clinical gout within the last year
   i. Hemoglobinopathy, including, but not limited to, thalassemia major
   j. Myelodysplastic syndromes
   k. Coagulopathy including, but not limited to hemophilia
   l. Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair
   m. Poor venous access that precludes routine peripheral blood sampling required for this study
   n. Subjects with indwelling venous catheters
   o. Subjects with a history of gastric surgery (eg, stapling, bypass) or subjects with a history of malabsorption disorders (eg, celiac sprue disease)
10. Evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years (except adequately treated carcinoma in situ and basal cell carcinoma of the skin). Subjects under evaluation for malignancy are not eligible.
11. Subjects who are pregnant or nursing. Subjects who intend to become pregnant during the study period. Male subjects with partners who are, or intend to become, pregnant during the study period.
12. Any other condition which, in the opinion of a physician investigator, would make the subject unsuitable for enrollment or could interfere with the subject participating in and completing the study.
13. Subjects who are part of the site personnel directly involved with this study.

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14. Subjects who are family members of the investigational study staff.
15. Subjects who had life-threatening serious adverse event (SAE) during screening period.

Laboratory Exclusion Criteria:

Note: If any of the laboratory exclusion criteria are met, then the site may have the subject retested. If a single value is within 10% of the listed laboratory exclusion criterion value, and the value is considered not to be clinically significant by the physician investigator, the subject may be considered for enrollment.

16. Hematologic, biochemical, and serologic criteria (growth factors may not be used to achieve study entry requirements):
    a. Hemoglobin (Hgb) <12 g/dL for females and <13 g/dL for males
    b. Neutrophils <1500/mm^3 (blacks/African-Americans: <1200/mm^3)
    c. Platelets <100,000/mm^3
    d. Direct bilirubin >1.5 x upper limit of normal (ULN) of the laboratory reference range. Total bilirubin >1.6 mg/dL unless the subject has a history of Gilbert's disease. If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart
17. Serum albumin < lower limit of normal (LLN) of laboratory reference range.
18. Thyroid-stimulating hormone (TSH) >1.2 x ULN or <0.8 x LLN of laboratory reference range with the following exceptions:
    a. the subject may be enrolled if clinically euthyroid, AND
    b. the euthyroid function is confirmed by thyroxine/triiodothyronine (T4/T3) testing.
19. Serum creatinine >ULN of the laboratory reference.
20. Serum glucose:
    a. For subjects not previously diagnosed with diabetes mellitus:
        i. ≥140 mg/dL (nonfasting) unless hemoglobin, A1c subtype (HbA_{1c}) ≤7% OR
        ii. ≥100 mg/dL (fasting) unless HbA_{1c} ≤7%
    b. For subjects previously diagnosed with diabetes mellitus, HbA_{1c} >8.5%
21. Prothrombin time/partial thromboplastin time (PT/PTT values) >10% above laboratory reference range.
22. Anti-nuclear antibodies (ANA) >1:320.
23. Alpha fetoprotein (AFP):
    a. AFP >100 ng/mL OR
    b. AFP 50 to 100 ng/mL requires a liver ultrasound and subjects with findings suspicious for HCC are excluded.

Test Product, Dose, Mode of Administration: Boceprevir (SCH 503034) 200 mg capsules, 800 mg TID PO.

Reference Therapy, Dose, Mode of Administration: PegIntron 1.5 μg/kg/week SC, weight-based ribavirin 600 mg/day to 1400 mg/day PO divided twice daily (BID).

Duration of Treatment:

Arms 1 and 3: 48 weeks of treatment with 24 weeks of post-treatment follow-up.

Arm 2: 28 weeks of treatment with 44 weeks of post-treatment follow-up and 48 weeks of treatment with 24 weeks of post-treatment follow-up based on detectability of HCV-RNA at Treatment Week 8 (TW 8).

Criteria for Evaluation:

Primary Endpoint: The primary efficacy endpoint is the achievement of SVR defined as undetectable plasma HCV-RNA at Follow-up Week (FW) 24. If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR. Subjects will be declared treatment failures in one of the following ways:

- Subjects in any treatment arm with detectable HCV-RNA at FW 24.
- Subjects in any treatment arm with detectable HCV-RNA at TW 24.
- Subjects in any treatment arm who are missing their HCV-RNA at FW 24 with detectable HCV-RNA at FW 12.

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Key Secondary Endpoint: The key secondary efficacy endpoint is the achievement of SVR defined as undetectable HCV-RNA FW 24 in non-Black/African American randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

Secondary Endpoints: The secondary efficacy endpoints in this study are:

- The proportion of subjects with early virologic response (eg, undetectable plasma HCV-RNA at Treatment Weeks [TW] 2, 4, 8, and 12) in subjects who achieve SVR.
- The proportion of subjects with undetectable HCV-RNA at FW 12.
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization.

Statistical Methods: The primary efficacy and safety analyses will be based on data from all randomized non-black/African American subjects who receive at least one dose of study medication ***(Full Analysis Set, FAS)***. The data for the black/African American population will be summarized separately.

The primary efficacy endpoint, the achievement of SVR, will be summarized using descriptive statistics (n, %) for each treatment arm.

Specific statistical methods to be used are presented below:

All primary statistical comparisons will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

Primary Efficacy Analysis:

The primary efficacy analysis will be carried out to evaluate the primary objective of the trial, and will be based on the FAS (all non-black/African American randomized subjects who receive at least one dose of any study medication [PegIntron, Ribavirin, or Boceprevir/Placebo]).

Key Secondary Efficacy Analysis:

The key secondary efficacy analysis will be carried out to evaluate the key secondary objective of the trial. The SVR rate will be summarized using descriptive statistics (n, %) for each of the three treatment arms in the mITT data set (non-black/African American randomized subjects who receive at least one dose of boceprevir [for the experimental therapy arms] or placebo [for the control arm]). All statistical comparisons for the key secondary efficacy analysis will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors). In order to control the type 1 error for the two comparisons (Arm 3 vs. Control, and Arm 2 vs. Control) for the primary analysis, a step down approach will be taken to carry out the statistical hypothesis testing, in which the 48 week experimental group (Arm 3) will be first compared against the control arm using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, efficacy of 48 weeks of treatment with boceprevir over the PegIntron/ribavirin group will be established. Next the 28/48 week experimental group (Arm 2) will be compared against the control arm using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28/48 week arm will be established.

To account for multiplicity between the primary and key-secondary analyses, we will step down to the key-secondary analyses only if the significance of the primary comparisons has been established.

A step-down approach will be used to control the type 1 error for the two key-secondary comparisons. First, the 48 week experimental group (Arm 3 for subjects who have received at least one dose of boceprevir) will be compared against the control arm (for subjects who have received at least one dose of placebo) using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, the next comparison will be carried out, ie, the 28/48 week experimental group (Arm 2 for subjects who have received at least one dose of boceprevir) will be compared against the control arm (for subjects who receive at least one dose of placebo) using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28/48 week arm will be established.

Secondary Efficacy Analyses:

The difference in the SVR rates among subjects with undetectable HCV-RNA level at TW 8 (4 weeks of boceprevir) and then treated for a total of either 24 weeks or 44 weeks of boceprevir will be summarized using a 95% confidence interval of the difference of proportions (obtained using Normal approximation for binary data).

The relationship between an early virologic response (ie, undetectable plasma HCV-RNA at TW 2, 4, 8, and 12) and SVR will be summarized by the proportion of subjects with undetectable HCV-RNA at these time points that achieved SVR.

The statistical methods used in the primary analyses will be repeated for the secondary efficacy endpoints that are binary; eg, virologic response rates at FW 12 and at 72 weeks post randomization.

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The relationship between virologic response at FW 12 and 72 weeks post-randomization to SVR will be assessed by the proportion of subjects who have undetectable HCV-RNA at these time points (FW 12 and 72 weeks postrandomization) and are also classified as having achieved SVR.

The effect of interferon (PEG + RBV) response during the first 4 weeks of lead-in on the SVR rate will be assessed by summarizing the change from baseline in the log_{10} viral load at TW 4 (categorized as <1 log_{10}-drop, 1 to 5 log_{10}-drop, etc) and the SVR rate among subjects in these various categories.

All secondary analyses will be performed on the FAS and the mITT set.

Phase and Visit Schedule:

After successful screening, all qualified subjects will be randomized to 1 of 3 treatment arms.

All subjects will initiate therapy with 4 weeks of PEG + RBV (WBD) treatment ("lead-in period").

After the 4 week lead-in period, boceprevir or placebo will be added, based upon arm to which the subject is randomized.

At the end of treatment all subjects will enter follow-up, whose length will vary depending on the arm to which they were randomized.

PROTOCOL DETAILS

STUDY OBJECTIVES

Primary Objective

The primary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg TID orally (PO) (hereafter called boceprevir) in combination with PegIntron™ 1.5 μg/kg QW subcutaneously (SC) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PEG + RBV WBD alone in previously untreated adult subjects with CHC genotype 1.

Key Secondary Objective

The key secondary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PEG + RBV (WBD) with the standard of care (PEG + RBV [WBD] alone) in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of boceprevir when used in combination with PEG + RBV (WBD).
- To define predictors of SVR, such as epidemiologic factors, disease characteristics, and on-treatment response.
- To develop the relationship between steady-state pharmacokinetic parameters, obtained from population-based pharmacokinetic model and responses in a subset of subjects.

OVERALL STUDY DESIGN AND PLAN

This is a randomized, multicenter study, double-blinded for boceprevir or placebo in combination with open-label PegIntron and ribavirin (WBD), in previously untreated adult subjects with CHC genotype 1. The primary efficacy endpoint is the achievement of SVR, defined as undetectable HCV-RNA at Follow-up Week (FW) 24. If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR. This study is projected to enroll a total of 1080 subjects at approximately 200 sites worldwide. The study will enroll 930 non-black/African American subjects (310:310:310 in Arms 1, 2, and 3, respectively). Additionally, a minimum of 150 black/African American subjects will also be enrolled in a 1:1:1 ratio among Arms 1, 2, and 3. There will be no upper limit on the number of black/African American subjects that can be enrolled in the study, but enrollment will be kept open for these subjects until the minimum of 150 black/African American subjects is achieved if that level is not reached at the time when 930 non-black/African Americans have been randomized.

Design of the Study

This is a randomized, multi-center study, double-blinded for boceprevir or placebo in combination with open-label PEG + RBV (WBD) in previously untreated adult subjects with CHC genotype 1 to be conducted in conformance with Good Clinical Practice (GCP).

4 Week PEG + RBV Lead-In: All subjects will be randomized to one of 3 treatment arms on Day 1. All subjects will receive 4 weeks of PEG+ RBV (WBD) prior to having boceprevir or placebo added to their regimen.

Control

- Arm 1: PEG 1.5 μg/kg + RBV (WBD) for 4 weeks followed by placebo + PEG 1.5 μg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

Experimental Therapy

- Arm 2: PEG 1.5 μg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 μg/kg + RBV (WBD) for 24 weeks. At the Treatment Week (TW) 28 visit, the interactive voice response system (IVRS) will assign subjects to one of two groups based on their HCV-RNA results on and after TW 8.

    1. At the TW 28 visit, subjects whose HCV-RNA was undetectable at TW 8 and at all subsequent assays will be instructed that they have completed their assigned treatment with boceprevir + PEG 1.5 μg/kg + RBV (WBD) and should proceed to 44 week follow-up. Sites and subjects will remain blinded as to their treatment arm until TW 28.

    2. At the TW 28 visit, subjects with detectable HCV-RNA at TW 8 or at any subsequent assays will be assigned by IVRS to continue on therapy with PLACEBO + PEG 1.5 μg/kg + RBV (WBD) for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up. The switch from boceprevir to placebo will occur in a blinded fashion.

- Arm 3: PEG 1.5 μg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 μg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

For All Subjects

Subjects in any treatment arm who have detectable and quantifiable HCV-RNA at Treatment Week (TW) 24 will be considered to have failed treatment. These subjects should return for an early termination (ET) visit as soon as possible, but not later than TW 28. Sites will be notified by the IVRS whether the subject is eligible for another study (subjects from Arm 1; see below for further details), or if the subject should proceed to the follow-up phase of this study (subjects from Arms 2 and 3).

- If these subjects have detectable HCV-RNA at TW 24, but the HCV-RNA is NOT quantifiable (eg, HCV-RNA <25 IU/mL, but HCV-RNA detected), and the subject previously had undetectable HCV-RNA, then these subjects may have their HCV-RNA re-assayed prior to determining if they must undergo an ET visit. This visit should occur as soon as possible so that treatment decisions can occur in a timely manner. These subjects should continue their assigned treatment and then return for an unscheduled visit as soon as repeat HCV-RNA results are available. Any subject whose HCV-RNA is again detectable must undergo an ET visit. Subjects whose HCV-RNA is undetectable on retest will be allowed to continue in treatment, and the detectable but non-quantifiable HCV-RNA will be considered a false positive (Table 3)

- If, in the opinion of the investigator, any subject's HCV-RNA result does not appear to be accurate based upon that subject's prior HCV-RNA levels, they may request that the laboratory retest the sample, or they may have the subject return to collect another sample as soon as possible so that treatment decisions can occur in a timely manner.

Table 3 Guidelines for application of Treatment Week 24 Rule

Week 20[a]	Week 24	Outcome	Note
HCV-RNA (ANY results)	HCV-RNA ≥25 IU/mL	Subject discontinues	Subject should proceed to follow-up
HCV-RNA detectable	HCV-RNA <25 IU/mL, but detectable	Subject discontinues	Subject should proceed to follow-up
HCV-RNA undetectable	HCV-RNA <25 IU/mL, but detectable	Subject may have HCV-RNA re-assayed	If on re-assay, HCV-RNA is detectable at any level, subject must be discontinued

HCV-RNA = Hepatitis C virus-ribonucleic acid.

a: For subjects whose HCV-RNA viral load is not available for TW 20, TW 16 is acceptable

Subjects who terminate therapy in the study prior to the last scheduled treatment visit should perform an ET visit. At an ET visit, all study-related procedures and labs for a TW 48/ET (ET) visit must be performed.

Control Arm Subjects

- Control Arm subjects (Arm 1) with detectable HCV-RNA at TW 24 will be offered the opportunity to receive treatment with boceprevir + PEG 1.5 μg/kg + RBV via an access study or to proceed to the follow-up phase of this study. Their physician will discuss the risks/benefits of participating in this access study with the subject based upon the most recently available data. If they decline to participate in the access study they will proceed to the follow-up phase of this study.

Participation in and Completion of the Study

The subject is considered to be enrolled in the study when the subject provides written informed consent. The subject is considered to have completed the study upon the completion of the last protocol-specified contact (eg, visits or telephone contacts). Subject participation may be terminated prior to completion. For those subjects who do not complete the study, subject participation will be considered terminated upon the completion of the last visit (eg, phone contact with the investigator or qualified designee). Subjects who terminate participation in the study prior to their last scheduled treatment visit should perform an ET visit.

Study Population

Adult subjects with CHC genotype 1 who have not received treatment previously for CHC. The subjects must meet all the inclusion criteria and none of the exclusion criteria to receive treatment assignment.

Subject Inclusion Criteria

The subject must meet ALL the criteria listed below for entry:

Inclusion Criteria for CHC

1. Subject must have previously documented CHC genotype 1 infection. Subjects with other or mixed genotypes are not eligible. The HCV-RNA result obtained from the central laboratory at the Screening Visit must confirm genotype 1 infection and be ≥10,000 IU/mL.

2. Subject must have a liver biopsy with histology consistent with CHC and no other etiology. Copies of the pathology report and histology slides (suitable for evaluation by the study central pathologist) are required for the subject to be included in the study. The slides and the pathology report must be available at the study site prior to subject randomization. Using the Scoring Systems for Hepatic Fibrosis, the investigator must determine the level of fibrosis demonstrated by the biopsy.

   Two unstained slides are preferred for reading by central pathologist selected by the sponsor; however, one slide stained with hematoxylin plus eosin (H & E) plus one slide stained with Masson's trichrome will be accepted (slides should be reviewed by the investigator to confirm adequacy). The central pathologist reading will be used for analysis purposes only; randomization will be performed based upon the local report.

   a. No cirrhosis: Biopsy must be within 3 years of the Screening Visit. For biopsies performed more than 18 months prior to the Screening Visit, fibrosis marker testing will be performed to assess level of fibrosis, as multiple studies have shown that such testing correlates well with liver biopsies in predicting degree of fibrosis.

   b. Cirrhosis: Any historic liver biopsy demonstrating cirrhosis will be sufficient regardless of length of time since biopsy.

c. Subjects whose timing of liver biopsy does not meet the criteria for subject eligibility may have a liver biopsy performed between Screening Visit and Day 1 after the Screening evaluation confirms that the subject meets the study inclusion criteria.

3. Subjects with bridging fibrosis or cirrhosis must have an ultrasound within 6 months of the Screening Visit (or between Screening and Day 1) with no findings suspicious for hepatocellular carcinoma (HCC).

General Inclusion Criteria

4. Subject must be ≥18 years of age.

5. Subject must weigh between 40 kg and 125 kg.

6. Subject and subject's partner(s) must each agree to use acceptable methods of contraception for at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug, or longer if dictated by local regulations.

7. Subjects must be willing to give written informed consent.

Subject Exclusion Criteria

The subject will be excluded from entry if ANY of the criteria listed below are met:

Clinical Exclusion Criteria

1. Subjects known to be coinfected with the human immunodeficiency virus (HIV) or hepatitis B virus (HBsAg positive).

2. Subjects who received prior treatment for hepatitis C; other than herbal remedies, except those with known hepatotoxicity (which are exclusionary). All herbal remedies used for hepatitis C treatment must be discontinued before Day 1. Only silymarin (milk thistle) is allowed during the study.

3. Treatment with any investigational drug within 30 days of the randomization visit in this study.

4. Participation in any other clinical trial within 30 days of randomization or intention to participate in another clinical trial during participation in this study. Collection of additional blood, urine, or tissue samples or additional data, beyond that specified in this protocol, is prohibited (other than that related to subject's medical care).

5. Evidence of decompensated liver disease including, but not limited to, a history or presence of clinical ascites, bleeding varices, or hepatic encephalopathy.

6. Diabetic and/or hypertensive subjects with clinically significant ocular examination findings: retinopathy, cotton wool spots, optic nerve disorder, retinal hemorrhage, or any other clinically significant abnormality.

7. Pre-existing psychiatric condition(s), including but not limited to:

   a. Current moderate or severe depression.

   b. History of depression associated with any of the following:

      i. Hospitalization for depression

      ii. Electroconvulsive therapy for depression

      iii. Depression that resulted in a prolonged absence from work and/or significant disruption of daily functions

   c. Suicidal or homicidal ideation and/or attempt.

d. History of severe psychiatric disorders (including but not limited to schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder or mania).

e. Past history or current use of lithium.

f. Past history or current use of antipsychotic drugs for those conditions listed in Exclusion Criterion No. 7d.

8. Clinical diagnosis of substance abuse of the following drugs within the following timeframes (not including time spent in detoxification, hospitalization, or incarceration):

a. Alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over-the-counter drugs: within 1 year of the Screening Visit OR

b. Multi-drug abuse (eg, 2 or more of the substances listed in Exclusion Criterion No. 8a): within 3 years of Screening Visit OR

c. Subjects receiving opiate agonist substitution therapy within 1 year of Screening Visit (except for those subjects monitored in an opioid substitution maintenance program)

OR

d. Subject's historic marijuana use is deemed excessive by a physician investigator or is interfering with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must be instructed to discontinue any current use of recreational marijuana prior to entry into study and throughout the study period.

9. Any known pre-existing medical condition that could interfere with the subject's participation in and completion of the study including but not limited to:

a. Central nervous system (CNS) trauma requiring intubation, intracranial pressure monitoring, brain meningeal or skull surgery, or resulting in seizure, coma, permanent neurologic deficits, abnormal brain imaging, or cerebral spinal fluid (CSF) leak. Prior brain hemorrhage and/or intracranial aneurysms (whether adequately repaired or not)

b. Current or history of seizure disorder unless seizure was >10 years ago, a single isolated event, no anti-seizure medications prescribed, and a normal neurological examination is documented in study files within 6 months of Day 1

c. History of stroke or transient ischemic attack

d. Immunologically-mediated disease (eg, inflammatory bowel disease [Crohn's disease, ulcerative colitis], celiac disease, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, sarcoidosis, severe psoriasis requiring oral or injected treatment, or symptomatic thyroid disorder)

e. Chronic pulmonary disease (eg, clinical chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, sarcoidosis)

f. Current or history of any clinically significant cardiac abnormalities/dysfunction (eg, angina, congestive heart failure, myocardial infarction, pulmonary hypertension, complex congenital heart disease, cardiomyopathy, significant arrhythmia) including current uncontrolled hypertension or history of use of antianginal agents for cardiac conditions

g. Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the study

h. Active clinical gout within the last year

i. Hemoglobinopathy, including, but not limited to, thalassemia major

j. Myelodysplastic syndromes

k. Coagulopathy, including, but not limited to, hemophilia

l. Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair

m. Poor venous access that precludes routine peripheral blood sampling required for this study

n. Subjects with indwelling venous catheters

o. Subjects with a history of gastric surgery (eg, stapling, bypass) or subjects with a history of malabsorption disorders (eg, celiac sprue disease)

10. Evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years (except adequately treated carcinoma in situ and basal cell carcinoma of the skin). Subjects under evaluation for malignancy are not eligible.

11. Subjects who are pregnant or nursing. Subjects who intend to become pregnant during the study period. Male subjects with partners who are, or intend to become, pregnant during the study period.

12. Any other condition which, in the opinion of a physician, would make the subject unsuitable for enrollment or could interfere with the subject participating in and completing the study.

13. Subjects who are part of the site personnel directly involved with this study.

14. Subjects who are family members of the investigational study staff.

15. Subjects who had life-threatening serious adverse event (SAE) during screening period.

Laboratory Exclusion Criteria

Note: If any of the laboratory exclusion criteria are met, then the site may have the subject retested. If a single value is within 10% of the listed laboratory exclusion criterion value, and the value is considered not to be clinically significant by the physician investigator, the subject may be considered for enrollment.

16. Hematologic, biochemical, and serologic criteria (growth factors may not be used to achieve study entry requirements):

a. Hemoglobin <12 g/dL for females and <13 g/dL for males

b. Neutrophils <1500/mm^3 (blacks/African-Americans: <1200/mm^3)

c. Platelets <100,000/mm^3

d. Direct bilirubin >1.5 x upper limit of normal (ULN) of the laboratory reference range. Total bilirubin >1.6 mg/dL unless the subject has a history of Gilbert's disease. If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart

17. Serum albumin < lower limit of normal (LLN) of laboratory reference range.

18. Thyroid-stimulating hormone (TSH) >1.2 x ULN or <0.8 x LLN of laboratory reference range with the following exceptions:

a. The subject may be enrolled if clinically euthyroid, AND

b. The euthyroid function is confirmed by thyroxine/triiodothyronine (T4/T3) testing

19. Serum creatinine >ULN of the laboratory reference.

20. Serum glucose:

    a. For subjects not previously diagnosed with diabetes mellitus:

        i. ≥140 mg/dL (nonfasting) unless hemoglobin, A1c subtype (HbA_{1c}) ≤7% OR

        ii. ≥100 mg/dL (fasting) unless HbA_{1c} ≤7%

    b. For subjects previously diagnosed with diabetes mellitus, HbA_{1c} >8.5%

21. Prothrombin time/partial thromboplastin time (PT/PTT) values >10% above laboratory reference range.

22. Anti-nuclear antibodies (ANA) >1:320.

23. Alpha fetoprotein (AFP):

    a. AFP >100 ng/mL OR

    b. AFP 50 to 100 ng/mL requires a liver ultrasound and subjects with findings suspicious for HCC are excluded.

Subject Discontinuation Criteria

Study drug treatment must be terminated during the study for any of the following reasons:

- Subject with detectable HCV-RNA at TW 24;
- Suicidal or homicidal ideation or attempt;
- Severe depression (subjects meeting criteria for the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV™] Major Depressive Episode);
- Subject has a positive test for nonprescription opiates, methamphetamines, or cocaine;
- Request of the subject (subjects have the right to discontinue treatment at any time for any reason);
- Subject becomes pregnant during the study;
- A physician investigator feels it is in best interest of the subject to discontinue.

Study drug treatment may be terminated during the study for any of the following reasons:

- SAE assessed by the physician investigator as possibly or probably related to study drug. Investigator may continue the subject in the study, if it is deemed to be in the best interest of the subject to stay on the study treatment;
- Failure to comply with the dosing, evaluations, or other requirements of the study;
- Virologic breakthrough defined as:

  Any subject who achieves undetectable HCV-RNA and subsequently has an HCV-RNA >1,000 IU/mL.

- Incomplete Virologic Response/Rebound defined as:

  Any subject who has a 1 $\log_{10}$ increase in HCV-RNA from their nadir with an HCV-RNA >1,000 IU/mL; if both samples being compared were collected the same number of days after their last PEG injection. In cases where the time from PEG injection to HCV-RNA sample being collected is different for the 2 samples, a 2-$\log_{10}$ increase is required to meet this criterion.

If the investigator believes that the test indicating virologic breakthrough or incomplete virologic response/rebound is clinically questionable based upon the pattern of response, the subject may be asked to come in for repeat testing within 2 weeks to confirm the result. If a subject has virologic breakthrough or an incomplete virologic response/rebound while on therapy, the subject may be discontinued from boceprevir treatment and continued on PegIntron and ribavirin with appropriate clinical follow-up. Once breakthrough/rebound has been identified, genotypic resistance will be characterized by performing HCV-RNA sequencing on appropriate samples including those collected around the time of rebound as well as during the follow-up period.

It is the right and the duty of the investigator or subinvestigator to interrupt treatment of any subject if he/she feels that study discontinuation is necessary to protect the subject, or that there are unmanageable factors, that may interfere significantly with the study procedures and/or the interpretation of results.

If a subject discontinues prior to completion of the study, the reason for the discontinuation will be obtained. The date of the last dose of study medication and the date of the last assessment and/or contact will be obtained. This information will be documented in the appropriate section of the case report form (CRF). A follow-up contact (telephone or visit) will be arranged as appropriate.

At the time of discontinuation, every effort should be made to ensure all procedures and evaluations scheduled for the final treatment visit (TW 48/ET) are performed. For all discontinued subjects, AEs should be recorded and medication compliance should be assessed. Any returned study drug should be inventoried.

Study Treatments

- Boceprevir (SCH 503034) or placebo 200 mg capsules, 800 mg TID PO.
- PegIntron 1.5 μg/kg/week SC.
- Ribavirin (weight-based dosing) 600 mg/day to 1400 mg/day PO divided twice daily (BID).

Method of Treatment Assignment

Site personnel will call the IVRS at the Day 1 visit. Subjects will be randomly assigned to 1 of 3 treatment arms and be assigned a subject number by the IVRS. The sites, sponsor, and subject will be blinded to assignment. Randomization is based on a computer-generated random code provided by the sponsor's biostatistics department to the IVRS. Approximately 1080 subjects will be randomized to one of 3 treatment arms in a 1:1:1 ratio.

Stratification of randomized treatment assignment will be baseline viral load: high viral load (>400,000 IU/mL) versus low viral load (≤400,000 IU/mL) based upon Screening Visit HCV-RNA result, and on HCV genotype 1a infection versus HCV genotype 1b infection. Those subjects with genotype 1 who cannot be classified as only 1a or 1b will be randomly assigned to a treatment arm.

Prior to calling the IVRS, the investigator must confirm that:

- Written informed consent has been obtained;
- Screening Visit evaluations have been performed; and
- Required laboratory results are available and results are acceptable;
- All the inclusion criteria have been met;
- None of the exclusion criteria apply;

If the period from time of screening laboratory evaluations to Day 1 is more than 8 weeks, blood chemistry (complete nonfasting), hematology and serum pregnancy test (for females) must be redone and results reviewed prior to randomization.

Boceprevir treatment will be administered in a double blinded, placebo-controlled manner, and PEG + RBV (WBD) will be administered open-label.

Subject Randomization Number Assignment

Once a subject is determined to be eligible for the study, the site will call the IVRS to obtain a Subject Randomization Number and Treatment Assignment. Treatment should start as close as possible to the date of randomization, preferably on the same day.

PegIntron Dosing

It is preferable that the first dose of PegIntron (Day 1) be administered under the direction of site personnel. Subjects will be taught to administer the SC injections. While it is recommended that PegIntron be administered on the same day each week, it is permissible for subjects to change their assigned day for dosing PegIntron, at the discretion of site personnel. Subjects should rotate their dose of PegIntron 1 day per week until they reach their desired dosing day. The PegIntron dose will be based upon the subject's weight at Day 1 and will be administered once weekly SC, using the Redipen® injection volumes shown in **Table 4** (for Arms 1, 2, and 3).

The use of the Redipen device is as instructed by site personnel. Alternate strength Redipens to deliver similar doses are permitted. In the event that the Redipen is not used, the sponsor will provide PegIntron in vials (and sterile water for injection) that allow for dosing equivalent to the Redipen. Reconstitution and injection instructions for the vial, if supplied, will be provided.

Table 4 PegIntron (1.5 mcg/kg QW) Dosing for Arms 1, 2, and 3

Body Weight, kg (lb)[a]	PEGINTRON Redipen® or Vial Strength to Use[b]	Amount of PegIntron (μg) to Administer	Volume (mL) of PegIntron to Administer
40 to 50 (88 to 110)	80 μg per 0.5 mL	64	0.4
>50 to 60 (>110 to 132)		80	0.5
>60 to 65 (>132 to 143)	120 μg per 0.5 mL	96	0.4
>65 to 75 (>143 to 165)			
>75 to 80 (>165 to 176)		120	0.5
>80 to 85 (>176 to 187)			
>85 to 105 (>187 to 231)	150 μg per 0.5 mL	150	0.5
>105 to 125 (>231 to 275)			

a: Use standard rounding procedures: for 0.1 to 0.4 kg, round down and 0.5 to 0.9 kg, round up.

b: It is anticipated that Redipens will be available for all PegIntron dosing. However, in the unlikely event that specific dosing pen sizes are not available, alternative strength Redipens delivering similar doses are indicated.

Ribavirin Dosing

Ribavirin will be administered BID orally with food. Ribavirin dose will be determined based on subject's weight at Day 1, as shown in Table 5.

Table 5 Ribavirin (600 to 1400 mg/day PO divided BID Regimen) Dosing for All Arms

Body Weight, kg (lb)	Ribavirin Daily Dose	200 mg Ribavirin Number of Capsules[a]
40 to 50 (88 to 110)	600 mg/day	1 capsules AM 2 capsules PM
>50 to 60 (>110 to 132)	800 mg/day	2 capsules AM 2 capsules PM
>60 to 65 (>132 to 143)		2 capsules AM 2 capsules PM
>65 to 75 (>143 to 165)	1000 mg/day	2 capsules AM 3 capsules PM
>75 to 80 (>165 to 176)		2 capsules AM 3 capsules PM
>80 to 85 (>176 to 187)	1200 mg/day	3 capsules AM 3 capsules PM
>85 to 95 (>187 to 209)		3 capsules AM 3 capsules PM
>95 to 105 (>209 to 231)		

>105 to 125 (>231 to 275)	1400 mg/day	3 capsules AM 4 capsules PM

a: AM and PM doses may be switched.

Boceprevir/Placebo Dosing

The dosing of boceprevir/placebo is three times daily. This may be accomplished with an 8 hour dosing regimen (Q8H) or with an asymmetric dosing schedule, as suggested in Table 6, with 7 hours between the morning dose and afternoon dose, 8 hours between afternoon and evening dose, and 9 hours between the evening and next morning dose (eg, 7 AM, 2 PM, and 10 PM). It is permissible for the actual hours of dosing administration to be altered to accommodate a subject's schedule, but dosing intervals of 7 to 9 hours are to be maintained.

Table 6. Examples of Asymmetric Dosing Schedules for Boceprevir/Placebo (Modified to Every 7 to 9 Hours)

AM Dose	Afternoon Dose	Evening Dose
6 AM	1 PM	9 PM
7 AM	2 PM	10 PM
8 AM	3 PM	11 PM
9 AM	4 PM	12 midnight

It is critical that subjects understand the importance of maintaining their dosing schedule. Subjects are to be instructed not to miss any doses. The subject's dosing diary should ideally be filled out by the subject as they take their dose. These diaries are to be brought to every study visit for review of dosing compliance by study staff.

All doses of boceprevir/placebo are to be administered orally with food. Ideally boceprevir/placebo should be taken with a meal. A small snack, such as a piece of fruit or crackers, is adequate. Boceprevir/placebo will be dispensed in 200-mg capsules. Four capsules are to be administered at each dose, with a total of 12 capsules per day.

Guidelines for Missed Doses of Study Medication

PegIntron

If subjects realize they missed a dose within 4 days following the scheduled dose, then they should take the missed dose. The subject should take their next dose on their regular scheduled day.

If subjects realize they missed a dose on Days 5 or 6, then they should skip the missed dose and resume their normal dosing schedule. Subjects should not double the next dose in order to "make up" what has been missed.

Ribavirin

If subjects miss a dose of ribavirin, then they should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then these missed doses should be skipped, and the normal dosing schedule should be resumed. Subjects should not double the next dose in order to "make up" what has been missed.

Boceprevir/Placebo

If subjects miss a dose and realize this 2 or more hours before the next dose is due, they should take the assigned dose with food, and resume the normal dosing schedule. If it is less than 2 hours before the next dose, the missed dose should be skipped.

Blinding of Study Treatments

This is a double-blinded study for boceprevir. Unblinding by request of the investigator should occur only in the event of an emergency or adverse event for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. If the investigator must identify the treatment assignment of an individual subject, the investigator or qualified designee is to call the IVRS.

Unblinding performed by the IVRS at the request of the investigator is to be reported in writing by the investigator to the sponsor, including a written explanation of the reason why the blind was broken.

Dispensing

PegIntron and ribavirin will be dispensed to all subjects in an open-label manner. Subjects should be dispensed a quantity of ribavirin that will allow them to have an adequate supply until their next visit plus 1 week extra supply in case their visit is delayed. Instructions for dispensing of boceprevir/placebo and PegIntron will be provided by the IVRS at each visit. Sites will be instructed by the IVRS as to which kit numbers of boceprevir/placebo should be dispensed to each subject.

Upon dispensing to the subject, while in the subject's possession:

- Ribavirin *may* be stored at room temperature;
- PegIntron should be stored refrigerated;
- Boceprevir and matching placebo capsules *may* be stored at room temperature for up to 8 weeks.

Medications Prohibited Prior to Screening and During the Study

In addition to prohibited medications listed in the Exclusion Criteria, subjects are prohibited from taking any approved or investigational drugs for CHC (other than the study medications), or systemic immunomodulatory agents for the duration of the study period through the end of the assigned follow-up period. Medications not specified as prohibited are to be allowed during the study.

Procedures for Monitoring Subject Compliance

The site personnel must ensure accuracy when comparing the amount of study drug administered by the subject, as reflected in the dosing diary, to the amount of study drug returned by the subject. This will be performed by site personnel responsible for dispensing, return, and accountability of study medication. A physical count will be used to determine drug accountability. The number determined by this physical count of PegIntron Redipens/vials and the number of empty (or full) bottles of ribavirin and boceprevir/placebo, as well as a count of the number of capsules remaining in partially used bottles should be compared to the expected number of PegIntron Redipens/vials, ribavirin and boceprevir/placebo capsules/bottles remaining if the subject were to have taken all scheduled doses of study medications, as recorded in the dosing diary by the subject.

If a discrepancy is noted between the actual count performed by site personnel versus that which would be expected to be remaining as per subject diary records, the discrepancy must be discussed with the subject and the explanation must be documented at the time of the drug return.

Site personnel will maintain an ongoing record of the dispensing and return of all study medication for each subject, which will be verified by the sponsor's study monitor. Site personnel will be expected to call subjects within the 1 week of initiating boceprevir (or placebo) during TW 5 to confirm that subjects are able to comply with taking boceprevir (or placebo) as directed.

Study Schedule

All treatment visits must be scheduled based on the Day 1 visit date. If a subject is unable to attend his/her scheduled visit, this must be documented in the subject's file and the site should request that the subject return as close to the scheduled visit date as possible.

Study Procedures

All scheduled laboratory evaluations will be performed by central laboratories selected by the sponsor. Site personnel will send all blood samples to the central laboratory by shipping them in the laboratory kits supplied. All clinical and laboratory evaluations and procedures related to inclusion/exclusion criteria, or performed during treatment, must be reviewed by an investigator who is a physician.

Clinical Evaluations

- Adverse Events

During the screening period, only SAEs should be recorded.

The principal investigator or sub-investigator (physician, physician assistant or nurse practitioner) must determine the severity and relationship to study medication(s) of all AEs. A physician investigator must review, initial and date the severity of all AEs and their relationship to study medications when initial assessment of an AE is made by a physician assistant or nurse practitioner. Designated medical practitioners must be licensed (as defined by local regulations) and the responsibilities transferred to them must be documented in the site file.

- Birth Control Confirmation

  Extreme care must be taken to avoid pregnancy in female subjects of childbearing potential and female partners of childbearing potential of male subjects.

  Subject and subject's partner(s) must each use acceptable methods of contraception 2 weeks prior to Day 1 and at least 6 months (or longer if dictated by local regulations) after last dose of study drug.

  Confirmation must be obtained by site personnel that subjects and their partner(s) are practicing dual contraception. Dual contraception requires that both partners use an effective birth control method. This assessment must be documented in the subject's study chart at each specified visit ().

  Females: Females must be using one of the following methods of birth control:

  a. Tubal ligation,

  b. Hormonal intrauterine device (IUD),

     Subjects with preexisting non-hormonal intrauterine devices who were enrolled prior to Protocol Amendment 1 will not be required to change birth control methods because of the risk of removal and insertion.

  c. Appropriate contraception registered for marketing containing an estrogen and/or progesterone agent (oral, transdermal, intramuscular, or implant).

     If it is permitted by local regulations, females may also fulfill this requirement by using one of the following (*not permitted for German sites*):

  d. Diaphragm,

  e. Sponge and spermicide *(not permitted for Canadian sites).*

  OR

  Females must either be:

  a. Postmenopausal,

  b. Surgically sterile (hysterectomy),

  c. Abstinent from sexual activity.

  Males: Sexually active males must be practicing acceptable methods of contraception (vasectomy or condom plus spermicide). The female partner(s) must also be practicing an acceptable method of contraception (see above).

- Chest X-ray

  Chest x-ray (posterior to anterior [PA] and lateral) must be performed within 6 months prior to the Screening Visit (or between the Screening Visit and Day 1) and may be performed at any time during the study if clinically indicated. Results will be captured in

the subject's study chart and not in the electronic case report form (eCRF). However, clinically significant findings from the screening chest x-ray report must be captured in the medical history eCRF. For chest x-rays performed during treatment or during the follow-up period, any clinically significant changes compared with the screening chest x-ray must be captured as AEs.

- Concomitant Medications

  All medication taken by the subject within two weeks prior to the Screening Visit and all concomitant medications taken by the subject during the study must be recorded.

- Dosing Diary Review

  Dosing diaries will be used to collect individual subject dosing data. At each visit, site personnel designated to dispense/collect/reconcile study medications must review the dosing diary for completeness and accuracy. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the dosing diary by comparing entries with amounts of returned study medication. If a discrepancy is noted, site personnel must discuss the discrepancy with the subject, and the explanation must be documented.

- Early Termination

  At the time of discontinuation, every effort should be made to ensure all procedures and evaluations scheduled for the final study visit (TW 48/ET) are performed. At an ET visit, all study related procedures and labs for an end of treatment (EOT) visit must be performed. ET subjects, with exclusion of Arm 1 subjects who choose to participate in another, should complete the 24 week follow-up schedule: FW 4, 12, and 24.

  All subjects, including subjects who discontinue early, will participate in the study for a total of 72 weeks (treatment plus follow-up). After completing follow-up, all subjects, including those who early terminated, will be offered an opportunity to participate in a long term follow-up study.

  For any subjects discontinuing treatment earlier than the assigned duration (early terminated), additional visits after FW 24 should be performed at least every 12 weeks as needed until a total of 72 weeks (treatment plus follow-up) is completed. In between each additional follow-up visit, a phone contact should be made every 6 weeks if their next scheduled follow-up visit is more than 6 weeks away.

- Electrocardiogram (12-Lead ECG)

  An ECG must be performed within 6 months prior to the Screening Visit (or between the Screening Visit and Day 1) and may be performed at any time during the study if clinically indicated. For ECGs performed during treatment or during the follow-up period, any clinically significant changes compared with the screening ECG must be captured as AEs.

- Height Assessment

- Inclusion/Exclusion Criteria Review

  The Inclusion and Exclusion Criteria must be reviewed by a physician investigator to ensure that the subject qualifies for the study.

- Informed Consent

  The principal investigator or sub-investigator (physician, physician assistant or nurse practitioner) will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent in a language in which the subject is fluent before

performing any study-related procedure. A signed copy of the informed consent must be given to the subject.

- Interactive Voice Response System (IVRS)

  Subjects who meet inclusion/exclusion criteria must be registered with the IVRS at the screening visit. Subjects will be randomized to one of the three study arms. All subjects will be assigned a randomization number at the Day 1 visit. The IVRS must be called at each visit as designated on the visit flow charts and IVRS will assign treatment with PegIntron Redipens and kit numbers for boceprevir/placebo at each visit.

- Liver Biopsy

  Subject must have a liver biopsy with histology consistent with CHC and no other etiology. Copies of the pathology report and histology slides (suitable for evaluation by the study central pathologist) are required for the subject to be included in the study. The slides and the pathology report must be available at the study site prior to subject randomization. Using the Scoring Systems for Hepatic Fibrosis, the investigator must determine the level of fibrosis demonstrated by the biopsy. Two unstained slides are preferred for reading by central pathologist selected by the sponsor; however, one slide stained with H & E plus one slide stained with Masson's trichrome will be accepted (slides should be reviewed by the investigator to confirm adequacy). The central pathologist reading will be used for analysis purposes only; randomization will be performed based upon the local report.

  a. No cirrhosis: Biopsy must be within 3 years of the Screening Visit. For biopsies performed more than 18 months prior to the Screening Visit, fibrosis marker testing will be performed to assess level of fibrosis.

  b. Cirrhosis: Any historic liver biopsy demonstrating cirrhosis will be sufficient regardless of length of time since biopsy.

  c. Subjects whose timing of liver biopsy does not meet the criteria for subject eligibility may have a liver biopsy performed between Screening Visit and Day 1 after the Screening evaluation confirms that the subject meets the study inclusion criteria.

- Medical History/Demographics

  A medical history will be obtained by the principal investigator or sub-investigator (physician, physician assistant or nurse practitioner). If the subject's current medical care was provided at another institution or location, an effort must be made to obtain these outside records or to obtain a statement from his/her primary care physician to verify that the subject does not meet any of the exclusion criteria. This must be done prior to randomizing the subject into the study. Alcohol, drug and any substance abuse history should also be obtained and documented in the subject's study chart.

- Ocular Examination

  A complete ocular examination for all subjects with diabetes mellitus or hypertension must be performed within 6 months prior to the Screening Visit (or between the Screening Visit and Day 1) and may be performed at any time during the study if clinically indicated. This exam consists of basic ophthalmic assessments plus dilated funduscopic examination. The consultation report must summarize the ocular findings. Retinal photographs must be taken for subjects with retinal abnormalities that do not prohibit enrollment into this study. The results of these photographs must be documented in the consultation report. Any such abnormalities must be recorded as medical history in the eCRF. Retinal photographs are not required to be available at sites, but must be available upon request. Retinal photographs are not required for subjects with a normal dilated funduscopic exam as performed and documented by an ophthalmologist.

Additional ocular exams may be performed during the treatment and/or post-treatment follow-up phases of the study at the discretion the physician investigator.

- Physical Examination

  All physical examinations must be performed by the principal investigator or sub-investigator (physician, physician assistant or nurse practitioner).

  A complete physical examination includes the following assessments: general appearance, head, eyes (including funduscopy), ears/nose/ throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. Any significant changes between the Screening Visit and Day 1 should be noted in the Medical History eCRF. Any significant changes after randomization must be reported as AEs and entered on the Adverse Event eCRF.
- Screening Number Assignment

  After a subject signs the informed consent form, a Screening number will be assigned by the study site. The subject will be identified by this Screening number throughout the Screening phase.
- Subject Randomization Number Assignment

  At Day 1, after ensuring that the subject meets all Inclusion and none of the Exclusion Criteria, site personnel will call the IVRS, which will randomize subjects to a treatment arm and assign each subject number which will be unique across the entire study.
- Telephone Contact

  Site personnel will be expected to call subjects within one week of initiating boceprevir (or placebo) during TW 5 to confirm that subjects are able to comply with taking boceprevir/placebo as directed.

  During follow-up, subjects should be contacted by phone between scheduled visits to be reminded of the importance of making their scheduled follow-up visits on time. All attempts should be made to contact those subjects who do not return for the follow-up visits. Attempts to contact the subject in the event of a "no-show" must be documented.
- Ultrasound

  Subjects who have bridging fibrosis or cirrhosis must have an ultrasound within 6 months of the Screening Visit with no findings suspicious for HCC, or if not available, ultrasound may be performed between Screening Visit and Day 1.
- Unscheduled Visits

  Unscheduled visits to ensure subject safety may be performed at any time at the discretion of the investigator.
- Vital Signs

  Blood pressure, pulse, and temperature will be measured and recorded. Clinically significant changes from Day 1 should also be captured as AEs in the eCRF.
- Weight Assessment

Laboratory Evaluations

- Alpha Fetoprotein (AFP)
- Anti-Nuclear Antibodies (ANA)
- Blood Chemistry (Abbreviated Nonfasting)

  Alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, total bilirubin (direct and indirect), urea nitrogen, total protein, albumin, uric acid, and glucose.

- Blood Chemistry (Complete Nonfasting)

ALT, AST, creatinine, alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin (direct and indirect), total protein, albumin, uric acid, urea nitrogen, glucose, HbA_{1c} (subjects with diagnosis of diabetes, whether on medication or diet controlled, and subjects with glucose above laboratory reference range), amylase, lipase, sodium, potassium, chloride, phosphorus, calcium, triglycerides, and cholesterol.

- HCV Genotype

  Subjects will be stratified based on screening visit genotype results. Plasma samples must be obtained and processed as instructed by the central laboratory selected by the sponsor.

- HCV-RNA Polymerase Chain Reaction (PCR)/HCV Sequence Analysis

  Plasma samples for HCV viral load must be obtained and processed as instructed by the central laboratory.

  HCV-RNA viral load will be determined using the Roche COBAS TaqMan HCV/HPS Test, v2.0. The assay is a nucleic acid amplification test for the quantitation of HCV-RNA genotypes 1 through 6 in human serum or plasma, using the High Pure System Viral Nucleic Acid Kit for manual sample preparation and the COBAS TaqMan 48 Analyzer for amplification and detection. The Roche COBAS TaqMan HCV/HPS v2.0 assay has a linear range from 25 to 391,000,000 IU/mL. The assay has a limit of quantitation of 25 IU/mL and of detection of 9.3 IU/mL.

  Plasma samples obtained for hepatitis C virus-ribonucleic acid polymerase chain reaction (HCV-RNA PCR) are suitable for use for HCV sequence analysis. HCV sequence analysis will be performed as appropriate and will depend on HCV-RNA PCR results. A proportion of subjects in each arm of the study will have samples analyzed for the presence of sequence variants either known or suspected to confer resistance to boceprevir.

  If a subject has virologic breakthrough or an incomplete virologic response/rebound while on therapy, the subject may be discontinued from boceprevir treatment and continued on PegIntron and ribavirin with appropriate clinical follow-up. Once breakthrough/rebound has been identified, genotypic resistance will be characterized by performing HCV-RNA sequencing on appropriate samples including those collected around the time of rebound as well as during the follow-up period.

  - If subjects have detectable HCV-RNA at EOT, or at the last FU visit, but the HCV-RNA is NOT quantifiable (eg, HCV-RNA <25 IU/mL, but HCV-RNA detected), then these subjects may have a back-up sample tested by the central laboratory if the previous HCV-RNA result reported undetectable HCV-RNA.

  - TW 24 Futility Rule: If subjects have detectable HCV-RNA at TW 24, but the HCV-RNA is NOT quantifiable (eg, HCV-RNA <25 IU/mL, but HCV-RNA detected), and the subject previously had undetectable HCV-RNA, then these subjects may have their HCV-RNA re-assayed prior to determining if they must undergo an ET visit.

    Subjects may have a back-up sample tested by the central laboratory if the HCV-RNA results from the previous visit reported undetectable HCV-RNA.

    If there is insufficient sample for a retest, subjects may return for an unscheduled visit to have HCV-RNA re-assayed. This visit should occur as soon as possible so that treatment decisions can occur in a timely manner.

    Subjects should continue their assigned treatment and then return for an ET visit as soon as possible if detectable HCV-RNA is reported upon retest. Subjects whose HCV-RNA is determined to be undetectable on retest will be allowed to continue on

treatment, and the detectable but non-quantifiable HCV-RNA will be considered a false positive.

If, in the opinion of the investigator, any subject's HCV-RNA result does not appear to be accurate based upon that subject's prior HCV-RNA levels, they may request that the laboratory retest the sample, or they may have the subject return to collect another sample as soon as possible so that treatment decisions can occur in a timely manner.

- Hematology

  Hemoglobin (Hgb), hematocrit (HCT), red blood cell (RBC) count, mean corpuscular volume (MCV), red cell distribution width (RDW), reticulocyte count, white blood cell (WBC) count with differential, platelet count and other hematologic parameters as deemed appropriate.

- Prothrombin Time/Partial Thromboplastin Time (PT/PTT)

  If PT is not available then international normalized ratio (INR) is acceptable.

- Pregnancy Test (Females Only): All screening, treatment visits and follow-up visits that are ≤6 months of last dose of study medication.

  Serum Pregnancy Test: All visits except Day 1 or those that are >6 months from last dose of study medication.

  Urine Pregnancy Test: Urine pregnancy test must be performed locally with negative results prior to the first dose of study medication (Day 1). In addition, a self pregnancy test must be performed by female subjects of childbearing potential at approximately TWs 31, 37, and 43, as well as at FWs 8, 16, and 20 (if requested by the local approving authority). The results must be provided to the investigator and/or site personnel and should be recorded in the subject's study charts.

- Thyroid-Stimulating Hormone (TSH)

- Urine Drug Screen (Opioid Maintenance Subjects Only): All screening, treatment, and follow-up visits.

Efficacy

Primary Endpoint

The primary efficacy endpoint is the achievement of SVR, defined as undetectable plasma HCV-RNA at FW 24. If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR. Subjects will be declared treatment failures in one of the following ways:

- Subjects in any treatment arm with detectable HCV-RNA at FW 24.
- Subjects in any treatment arm with detectable HCV-RNA at TW 24.
- Subjects in any treatment arm who are missing their HCV-RNA at FW 24, with detectable HCV-RNA at FW 12.

Key Secondary Endpoint

The key secondary efficacy endpoint is the achievement of SVR defined as undetectable HCV-RNA FW 24 in non-black/African American randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and BOCEPREVIR for the experimental arms).

In order to evaluate the primary and key secondary objectives of the study, the SVR rate will be analyzed for the Full Analysis Set (FAS) and the Modified Intent-to-Treat (mITT) set.

Secondary Endpoints

The secondary *efficacy* endpoints are:

- The proportion of subjects with early virologic response (eg, undetectable HCV-RNA at TWs 2, 4, 8 or 12) who achieved SVR.
- The proportion of subjects with undetectable HCV-RNA at FW 12.
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization.

Safety

Specification of Safety Variables

The following variables will be evaluated as key safety parameters: dose discontinuations/modifications due to AEs, treatment-related SAEs, neutrophil count $<0.75 \times 10^9$/L, and Hgb <10 g/dL.

Assessment and Reporting of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, biologic (at any dose), whether or not considered related to the use of that product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. In addition, clinically significant laboratory abnormalities that meet one or several of the following criteria are considered AEs:

- Requires intervention/additional therapy;
- Requires a dose modification;
- Associated with a clinical manifestation.

Any laboratory abnormality considered clinically significant by a physician investigator must be noted as such on the hard copy of the lab report with the physician's initials and date reviewed. Any event that is associated with, or observed in conjunction with, a product overdose, whether accidental or intentional, or a product abuse and/or withdrawal is also considered an AE.

All AEs must be recorded in the subject's medical records and on the eCRF. The onset and end dates, severity and relationship to study drug will be recorded for each AE. The severity of the AE will be assessed according to specific guidelines. Any action or outcome (eg, hospitalization, discontinuation of therapy) will also be recorded for each AE.

Subjects will be questioned and/or examined by the principal investigator or a sub-investigator (physician, physician assistant, nurse practitioner). The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit"? The presence or absence of specific AEs should not be elicited from subjects.

Assessment of Adverse Event Severity and Relationship to Treatment

Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of the investigator, or, if the investigator is not a physician, a designated sub-investigator who is a physician, physician assistant or nurse practitioner.

The modified World Health Organization (WHO) grading system will be used for grading severity of AEs with the exception of laboratory values. A physician may use his/her clinical judgment in assigning severity to abnormal laboratory AEs using clinical criteria. For AEs not covered by this grading system, the following definitions will be used:

- Mild: awareness of sign, symptom, or event, but easily tolerated;
- Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;
- Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention;

- Life-Threatening: immediate risk of death.

An investigator (physician, physician assistant or nurse practitioner) must also assess the relationship of any AE to the use of study drug, based on available information (such as the IB), using the following guidelines:

- Unlikely related: no temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated;
- Possibly related: temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded;
- Probably related: temporal association, other etiologies are possible but unlikely.

A physician investigator must review, initial and date the severity and relationship of all AEs to study medications when initial assessment of an AE is made by a physician assistant or nurse practitioner.

For expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to Health Authorities and investigators all events with the causality assessment "possibly" or "probably" related to study drug will be considered as related to study drug (suspected events). All events with "unlikely" causality assessment will be considered as not related.

Monitoring Adverse Events

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by an investigator (physician, physician assistant or nurse practitioner). All AEs must be followed to satisfactory resolution or stabilization of the events. Any actions taken and follow-up results must be recorded on the appropriate page of the eCRF and in the subject's study chart. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically indicated until the final resolution or stabilization of the events.

Management of Adverse Events

Adverse events may be managed, in some cases, by dose reduction of PegIntron, ribavirin and/or boceprevir/placebo. In the case of serious or life-threatening AEs, PegIntron, ribavirin, and/or boceprevir/placebo may be discontinued or dose reduced. In the event that discontinuation or interruption of individual study drugs is necessary, the permissible/nonpermissible combination regimens are provided in Table 11. All regimens must include PegIntron; no subjects may be interrupted from PegIntron for >2 weeks.

It is the decision of a physician as to whether boceprevir/placebo, PegIntron or ribavirin requires dose reduction or discontinuation. Laboratory abnormalities, as listed in Table 10, may require dose reduction, dose interruption, or discontinuation unless an alternative plan is formulated. Reduced doses of boceprevir/placebo, PegIntron, and ribavirin can be achieved by decreasing the dose. This may require use of a different Redipen (or vial) strength than that originally assigned at Day 1. For dose reduction of PegIntron, dial-down of the Redipen is permissible, depending on PegIntron dose assigned.

While at the first reduced dose level, the subject should return for assessment at a recommended interval of every 1 to 2 weeks until the AE resolves or the subject is stable. If further dose reduction is required, the second (or third for ribavirin) level of dose reduction may be used. If the AE persists but does not fall into the range for discontinuation/treatment interruption, the reduced dose of boceprevir/placebo, PegIntron and/or ribavirin (whichever has been reduced) may be continued.

At the discretion of the physician, the dose of boceprevir/placebo, PegIntron, and/or ribavirin, may be increased to full dose directly or in steps, respectively, when the AE subsides.

Table 7 Dose Reduction of Boceprevir/Placebo

Protocol No. P05216

Original Assigned Dose of Boceprevir/Placebo	First Reduced Dose of Boceprevir/Placebo	Second Reduced Dose of Boceprevir/Placebo	Third Reduced Dose of Boceprevir/Placebo
boceprevir/placebo 800 mg TID	boceprevir/placebo 600 mg TID	boceprevir/placebo 400 mg TID	None – Subject must discontinue boceprevir/placebo treatment

TID = three times a day.

Table 8 Recommended Dose Reduction for PegIntron 1.5 mcg/kg
Protocol No. P05216

		First Reduced Dose (1.0 μg/kg)[a]			Second Reduced Dose (0.5 μg/kg)		
Weight at Day 1[b]		Pen Size	Volume for Injection (mL)	Dose (μg)	Pen Size	Volume for Injection (mL)	Dose (μg)
40 to 50 kg	88 to 110 lb	Redipen 50	0.45	45	Redipen 50	0.30	30
>50 to 60 kg	>110 to 132 lb	Redipen 80	0.35	56	Redipen 50	0.30	30
>60 to 65 kg	>132 to 143 lb	Redipen 80	0.40	64	Redipen 50	0.35	35
>65 to 75 kg	>143 to 165 lb	Redipen 80	0.45	72	Redipen 50	0.35	35
>75 to 80 kg	>165 to 176 lb	Redipen 80	0.5	80	Redipen 50	0.40	40
>80 to 85 kg	>176 to 187 lb	Redipen 120	0.35	84	Redipen 50	0.40	40
>85 to 95 kg	>187 to 209 lb	Redipen 120	0.40	96	Redipen 50	0.50	50
>95 to 105 kg	>209 to 231 lb	Redipen 150	0.35	105	Redipen 50	0.50	50
>105 to 125 kg	>231 to 275 lb	Redipen 150	0.35	105	Redipen 50	0.50	50

a: It is anticipated that Redipens will be available for all PegIntron dosing. However, in the unlikely event that specific dosing pen sizes are not available, alternative dose reduction parameters are provided.

b: Use standard rounding procedures: for 0.1 to 0.4 kg, round down and 0.5 to 0.9 kg, round up.

Table 9 Recommended Dose Reduction for Ribavirin
Protocol No. P05216

Weight at Day 1[a]		Full Daily Dose (mg/day)	First Reduced Dose (mg/day)	Number of Capsules for First Dose Reduction	Second Reduced Dose (mg/day)	Number of Capsules for Second Dose Reduction	Third Reduced Dose (mg/day)	Number of Capsules for Third Dose Reduction
40 to 50 kg	88 to 110 lb	600	400	1 in the AM/1 in the PM	200	1 in PM	Discontinue	none
>50 to 65 kg	>110 to 143 lb	800	600	1 in the AM/2 in the PM	400	1 in the AM/1 in the PM	200	1 in the PM
>65 to 80 kg	>143 to 176 lb	1000	800	2 in the AM/2 in the PM	600	1 in AM/2 in PM	400	1 in AM/1 in PM
>80 to 105 kg	>176 to 231 lb	1200	1000	2 in the AM/3 in the PM	800	2 in AM/2 in PM	600	1 in AM/2 in PM
>105 to 125 kg	>231 to 275 lb	1400	1000	2 in the AM/3 in the PM	800	2 in AM/2 in PM	600	1 in AM/2 in PM

a: Use standard rounding procedures: for 0.1 to 0.4 kg, round down and 0.5 to 0.9 kg, round up.

Management of Selected Hematologic and Biochemical Parameters

Table 10 Recommended Dose Reduction (PegIntron and Ribavirin) for Selected Hematologic and Biochemical Parameters
Protocol No. P05216

Parameter	Dose Reduction (Table 8 and Table 9)	Discontinuation or Interruption[a] of PegIntron/ribavirin Treatment
Hemoglobin	<10 g/dL (ribavirin)	<8.5 g/dL (ribavirin)
White Blood Cell Count	<1.5 x 10^9/L (PegIntron)	<1.0 x 10^9/L (PegIntron)
Neutrophil Count	<0.75 x 10^9/L (PegIntron)	<0.5 x 10^9/L (PegIntron)
Platelet Count	<50 x 10^9/L (PegIntron)	<25 x 10^9/L (PegIntron)
Creatinine		>2.0 mg/dL (>176.8 μmol/L)
ALT/AST		2 x baseline and >10 x ULN

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

a: Individual study drug regimen interruptions are permissible based on the results of abnormal laboratory parameters. Treatment interruptions should not exceed 2 consecutive weeks in duration.

In the event that discontinuation or interruption of individual study drugs is necessary, the permissible/nonpermissible combination regimens are provided in Table 11. All regimens must include PegIntron; no subjects may be interrupted from PegIntron therapy for >2 weeks.

Table 11 List of Permissible/Nonpermissible Study Drug Regimens Following Individual Study Drug Discontinuations

Protocol No. P05216

Study Drug Combination	Permissible
PegIntron plus Boceprevir	Yes
PegIntron plus Ribavirin	Yes
PegIntron Monotherapy	Yes
Boceprevir Monotherapy	No
Boceprevir plus Ribavirin	No
Ribavirin Monotherapy	No

Use of Hematopoietic Growth Factors

Erythropoietin (epoetin alfa) and/or granulocyte-colony stimulating factor (G-CSF) may not be used prior to initiating therapy with PegIntron/ribavirin/boceprevir for the purpose of achieving a hemoglobin level or white blood cell (WBC)/neutrophil count adequate to qualify for enrollment in the study.

The decision to use erythropoietin or G-CSF is a clinical decision and is permitted anytime after initiation of study medications. If the serum hemoglobin is ≤10 g/dL, corrective action should occur: reduction of ribavirin, or initiation of erythropoietin therapy or combination of both may be used. Guidelines for the use of erythropoietin are provided below:

- Initial dose of erythropoietin 40,000 units SC, QW. Due to limited experience, in this setting long-acting formulations (eg, darbepoetin alfa) cannot be used.
- Perform weekly monitoring of blood pressure and hemoglobin values after initiation of erythropoietin therapy. In order to receive timely hemoglobin values, local labs for complete blood counts (CBCs) can be used as appropriate.
- Do not use erythropoietin if serum hemoglobin ≥12 g/dL.
- If serum hemoglobin is stable between 10 to 12 g/dL on 4 consecutive weekly measures and the subject is receiving a stable dosing regimen of erythropoietin, then decrease the monitoring of blood pressure and hemoglobin to every 2 weeks, and then if stable to every 2 to 4 weeks. Reduce the dose of erythropoietin by 25% to 50% if hemoglobin levels increase by >1 g/dL within 2 weeks or >2 g/dL within 4 weeks.

Sponsor will make erythropoietin available to subjects as part of the protocol.

Management of Depression During Study

Subjects who develop mild depression during the study may continue their study medication and should be monitored weekly (by visit or by phone) for 4 to 8 weeks. If the subject's status is stable at that time, the subject may resume the normal visit schedule with instructions to call the study center immediately if the subject feels that the depression has worsened. If the subject's condition worsens, see instructions for moderate and/or severe depression below.

Subjects who develop moderate depression during the study should have their dose of PegIntron reduced (Table 8, at the discretion of the investigator [who is a physician] as to which of these two doses is used). Subjects should be monitored weekly (by visit or phone, at least two visits should be in the office) for 4 to 8 weeks (depending on the subjects' status) to assure that their status is stable. These subjects may remain on reduced PegIntron dosing if the condition is considered stable and does not interfere with the subject's normal activities. Other clinical management intervention may be instituted as necessary. Subjects will be instructed to call the study center immediately if they feel their depression has worsened. If the subject's condition worsens, the subject should immediately discontinue all study medication, and a physician should make a priority assessment of the severity of the subject's condition. Appropriate therapeutic measures should be instituted, and the subject should be followed weekly or biweekly (depending on the physician's clinical judgment) by visit or by phone until the subject's status has returned to baseline conditions.

A subject with severe depression according to the criteria outlined by DSM-IV or with suicidal and/or homicidal ideation/attempt must discontinue all study medications and receive such evaluation as deemed necessary by a physician, until depressive symptoms have improved to baseline conditions. All suicidal/homicidal ideation and/or attempts are to be reported as SAEs according to the timeframe specified. The subject should not resume therapy and should be followed until resolution of the symptoms. Subjects who discontinue treatment should be monitored as described in Subject Discontinuation Criteria.

Known Adverse Events Relating to the Underlying Clinical Condition

General medical complaints typically attributed to CHC consist of fatigue, right upper quadrant pain, flu-like symptoms, and headache. Hepatic manifestations of CHC include cirrhosis and evidence of liver decompensation, such as bleeding esophageal varices, coagulopathy, thrombocytopenia, jaundice, hypoproteinemic states with resultant ascites, edema, or anasarca and hepatic encephalopathy. HCC is also known to occur as a complication of long-standing CHC. Extra-hepatic manifestations of CHC include cryoglobulinemia, membranous and membranoproliferative glomerulonephritis, peripheral neuropathy, Raynaud's syndrome, vasculitis, and porphyria cutanea tarda. Less well confirmed potential associations with CHC are polyarteritis nodosa, Sjogren's syndrome, and lichen planus.

Definition of Serious Adverse Events

A serious adverse event (SAE) is any adverse drug or biologic or device experience occurring at any dose that results in any of the following outcomes:

- death;
- life-threatening AE (ie, one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs);
- persistent or significant disability/incapacity;
- requires in-patient hospitalization (ie, admission), or prolongs hospitalization;
- congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

In addition, laboratory value(s) changes meeting the definition of an SAE may require reporting unless otherwise specified. Grade 4 laboratory abnormalities that are not accompanied by clinical manifestations will NOT be considered SAEs. Out of normal range liver function tests are not unexpected in subjects with CHC and may not be SAEs, unless there is a significant elevation from baseline or evidence of hepatic failure.

All SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee to the sponsor's designated safety/compliance officer within 1 working day of first becoming aware of the event. If the report is given to the sponsor via telephone rather than in writing on the form designated for SAE reporting, a full description of the event and any sequelae, including the investigator-determined causality to the study drug must be provided, so that the appropriate written report can be completed by the designated sponsor contact. SAEs that occur at any time after the inclusion of the subject in the study up to 30 days after the subject completed or discontinued the study must be reported. In the specific circumstance of screen failures, SAEs must be collected from the time of consent signing until the subject is considered a screen failure.

For subjects with SAEs occurring during the screening portion of the study, all Screening Visit safety laboratories need to be repeated to confirm that the subject met all inclusion and exclusion criteria.

Reports of all SAEs must be communicated as soon as possible to the appropriate IRB or IEC and/or reported in accordance with local laws and regulations.

Reporting of Subject Death

The death of any subject after enrollment or within 30 days of study completion, regardless of the cause, must be reported by the investigator or qualified designee to the sponsor's designated safety/compliance officer within 1 working day of first becoming aware of the death. After the 30-day period, deaths need to be reported only for long-term survival studies. If the report is given via telephone rather than in writing on the form designated for SAE reporting, a full description of the circumstances, including the investigator-determined causality to the study drug must be provided, so that the appropriate written report can be completed by the designated sponsor contact.

Reports of all deaths must be communicated as soon as possible to the appropriate IRB or IEC and/or reported in accordance with local law and regulations. If an autopsy is performed, the report must be provided to the sponsor.

Reporting of Pregnancies

Pregnancy information on clinical study subjects is collected by the sponsor's Global Pharmacovigilance (GPV) department. If a subject, including the female partner(s) of a male study subject, becomes pregnant during the course of the study, the Investigator or site personnel must notify the sponsor's designated safety officer within 5 working days after the Investigator or site personnel first become aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (1 working day) must be met. The sponsor's representative will provide instructions on how to collect pregnancy information. Follow-up information on the outcome of the pregnancy should also be forwarded to the sponsor.

STATISTICAL AND ANALYTICAL PLANS

This section describes the planned statistical analyses for this study. A Data Analysis Plan (DAP), incorporating detailed statistical analysis methods and data handling rules, will be completed and filed prior to any unblinded analysis.

This is a multi-center, randomized, double-blinded study of boceprevir or placebo in combination with open-label PEG + RBV in previously untreated subjects with CHC infected with HCV genotype 1. Approximately 1080 subjects (930 non-blacks/non-African-Americans, and at least 150 blacks/African Americans) are expected to be randomized to the following three treatment arms in a 1:1:1 ratio:

- Arm 1: PEG 1.5 μg/kg QW + RBV (WBD) for 4 weeks followed by placebo + PEG 1.5 μg/kg QW + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

- Arm 2: PEG 1.5 μg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 μg/kg QW + RBV (WBD) for 24 weeks. At the TW 28 visit, IVRS will assign subjects to one of two groups based on their HCV-RNA results on and after TW 8.

    1. At the TW 28 visit, subjects whose HCV-RNA was <u>undetectable</u> at TW 8 and at all subsequent assays will complete their treatment with boceprevir + PEG 1.5 μg/kg + RBV (WBD) and proceed to 44 week follow-up. Sites and subjects will remain blinded as to their treatment arm until TW 28.

    2. At the TW 28 visit, subjects with <u>detectable</u> HCV-RNA at TW 8 or at any subsequent assays will be assigned by IVRS to continue on therapy with PLACEBO + PEG 1.5 μg/kg + RBV (WBD) for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up. The switch from boceprevir to placebo will occur in a blinded fashion.

- Arm 3: PEG 1.5 μg/kg QW + RBV (WBD) for 4 weeks followed by boceprevir+ PEG 1.5 μg/kg QW + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

Note: Subjects in any treatment arm who have detectable HCV-RNA at TW 24 will discontinue treatment by TW 28 and will be considered to have failed treatment for purposes of the primary analysis.

Data Sets

The primary efficacy and safety analyses will be based on data from all non-black/African American subjects randomized and who receive at least one dose of study medication *(Full Analysis Set, FAS)*.

The key secondary efficacy analysis will be based on the mITT defined as all non-black/African American randomized subjects who receive at least one dose of boceprevir (for the experimental therapy arms) or placebo (for the control arm). Subjects who discontinue during the 4 week lead-in will not be included in the mITT set. Secondary efficacy analyses and safety analyses will also be performed on this dataset.

The statistical analyses will also be conducted independent of each other for non-blacks/African Americans and for blacks/African Americans, and the results will be presented for each group.

Demographic and Other Baseline Characteristics

The baseline demographic and disease characteristics data will be summarized using descriptive statistics to assess comparability between the treatment groups within each part of the study. For categorical variables, numbers in each treatment group for all categories will be presented along with the percentages. For continuous variables, mean, median, minimum, maximum, and standard error for each treatment group will be presented.

Efficacy Analyses

The primary efficacy endpoint in this study is the achievement of SVR, defined as undetectable plasma HCV-RNA at FW 24. If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR.

Subjects will be declared treatment failures in one of the following ways:

- Subjects in any treatment arm who have detectable HCV-RNA at FW 24.
- Subjects in any treatment who have detectable HCV-RNA at TW 24.
- Subjects in any treatment arm who are missing their HCV-RNA viral load at FW 24 and have detectable HCV-RNA at FW 12.

The key secondary efficacy endpoint is the achievement of SVR defined as undetectable HCV-RNA FW 24 in non-black/African American randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

The secondary efficacy endpoints in this study are:

- The proportion of subjects with an early virologic response (eg, undetectable HCV-RNA at TWs 2, 4, 8, or 12) in subjects who achieve SVR.
- The proportion of subjects with undetectable HCV-RNA at FW 12.
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization.

Primary Efficacy Analysis:

The primary efficacy analysis will be carried out to evaluate the primary objective of the trial, and will be based on the FAS (all non-black/African American randomized subjects who receive at least one dose of any study medication [PegIntron, Ribavirin, or Boceprevir/Placebo]). The primary efficacy endpoint will be summarized (using descriptive statistics and large sample 95% confidence intervals) for each treatment group by the subsets of subjects defined by the stratification factors and also by key baseline and demographic characteristics. Statistical methods to be used are presented below.

All primary statistical comparisons will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

Key Secondary Efficacy Analysis:

The key secondary efficacy analysis will be carried out to evaluate the key secondary objective of the trial. The SVR rate will be summarized using descriptive statistics (n, %) for each of the three treatment arms in the mITT data set (non-black/African American randomized subjects who receive at least one dose of boceprevir [for the experimental therapy arms] or placebo [for the control arm]). All statistical comparisons for the key secondary efficacy analysis will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

In order to control the type 1 error for the two comparisons (Arm 3 vs. Control, and Arm 2 vs. Control) for the primary analysis, a step down approach will be taken to carry out the statistical hypothesis testing, in which the 48 week experimental group (Arm 3) will be first compared against the control arm using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, efficacy of 48 weeks of treatment with boceprevir over the PegIntron/ribavirin groups will be established. Next, the 28/48 week experimental group (Arm 2) will be compared against the control arm using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28*/48* weeks arm will be established.

To account for multiplicity between the primary and key-secondary analyses, we will step down to the key-secondary analyses only if the significance of the primary comparisons has been established.

A step-down approach will be used to control the type 1 error for the two key-secondary comparisons. First, the 48 week experimental group (Arm 3 for subjects who have received at least one dose of boceprevir) will be compared against the control arm (for subjects who have received at least one dose of placebo) using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, the next comparison will be carried out, ie, the 28/48 week experimental group (Arm 2 for subjects who have received at least one dose of boceprevir) will be compared against the control arm (for subjects who receive at least one dose of placebo) using the same CMH test. If this p--value is less than 0.05, then the efficacy of the 28/48 week arm will be established.

Secondary Efficacy Analyses:

The difference in the SVR rates among subjects with undetectable HCV-RNA level at TW 8 (4 weeks of boceprevir) and then treated for a total of either 28 weeks or 48 weeks will be summarized using a 95% confidence interval of the difference of proportions (obtained using Normal approximation for binary data).

The relationship between an early virologic response (ie, undetectable plasma HCV-RNA at TW 2, 4, 8, and 12) and SVR will be summarized by the proportion of subjects with undetectable HCV-RNA at these time points that achieved SVR.

The statistical methods used in the primary analyses will be repeated for the secondary efficacy endpoints that are binary; ie, virologic response rates at FW 12 and at 72 weeks post randomization.

The relationship between virologic response at FW 12 and 72 weeks post-randomization to SVR will be assessed by the proportion of subjects who have undetectable HCV-RNA at these time points (FW 12 and 72 weeks post-randomization) and are also classified as having achieved SVR.

The effect of interferon (PEG + RBV) response during the first 4 weeks of lead-in on the SVR rate will be assessed by summarizing the change from baseline in the $\log_{10}$ viral load at TW 4 (categorized as <1 $\log_{10}$ drop, 1 to 5 $\log_{10}$ drop, etc) and the SVR rate among subjects in these various categories.

All secondary analyses will be performed on the FAS and the mITT set. The data for the black/African American portion of the study will be summarized separately.

Procedures for Accounting for Missing Data

During the treatment period, any subject missing an HCV-RNA evaluation at any particular visit will be considered to be a nonresponder for that visit. As stated in the definition of the primary efficacy endpoint, subjects in any of the treatment arms who are missing HCV-RNA data at FW 24 and are not virologic responders (ie, undetectable HCV-RNA) at FW 12 will be considered treatment failures. If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR. For all treatment arms, if a subject with a missing assessment at FW 24 returns to the study center at a later time point with a HCV-RNA below the lower limit of detection, that subject will be

considered a sustained virologic responder provided the subject does not receive any other treatment for hepatitis C during the follow-up period.

Safety

The safety data will be summarized separately for each part of the study. The safety analyses will include all randomized subjects who receive at least one dose of study medication. The number of subjects reporting any AEs, the incident of specific AEs, and discontinuations due to AEs will be tabulated by treatment group. Laboratory data will be listed by the treatment group and values outside the normal range will be flagged. Vital signs (pulse, weight, etc) will be summarized by treatment group. The proportion of subjects with dose modification/discontinuation due to AEs, serious treatment-related AEs, neutrophil count $<0.75 \times 10^9$/L, and/or hemoglobin <10 g/dL will be examined.

Safety results will be reviewed by the Data Review Advisory Board (DRAB) Members.

Determination of Sample Size/Power/Level of Significance

This study is projected to enroll a total of 930 non-black/African American subjects (310:310:310) in Arms 1, 2, and 3, respectively. Additionally, a minimum of 150 black/African American subjects will be enrolled with no upper limit for enrollment. Enrollment for the study will close when 930 non-black/African American subjects are randomized and at least 150 black/African American subjects have been randomized.

For statistical comparisons, a step down approach will be taken, where the 48 week experimental group (Arm 3) will be compared against the control arm, and if that test is significant ($p<0.05$), the 28/48 week experimental group (Arm 2) will be compared against the control arm. All the primary efficacy analyses will be based on the data from the 930 non-black/African American subjects. With 310 subjects per arm, the study will have 90% power to detect a combined 13% improvement in the SVR rate, assuming a control SVR rate of 45% (ie, 58% vs 45%) using a 2-sided chi-square test at alpha = 0.05.

With 50 subjects per arm, the true response rate in the black/African American population can be estimated within ± 14% assuming an estimated response rate of 50% and using a 2-sided 95% confidence interval.

No interim analysis of the efficacy data is planned. Safety data will be reviewed by the DRAB on an ongoing basis.

SUPPLEMENTARY APPENDIX II

[Data Analysis Plan]

for

Boceprevir with Peginterferon and Ribavirin

For Chronic Hepatitis C

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SPRINT-2 [P05216]
DATA ANALYSIS PLAN

(Amendment 1: 26 March 2010)

TABLE OF CONTENTS

1. INTRODUCTION

This document provides a detailed statistical analysis plan for protocol P05216, a Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1. The study was designed to compare the efficacy of two therapeutic regimens of SCH 503034 (boceprevir) 800 mg TID in combination with PegIntron 1.5 µg/kg weekly plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO (hereafter called PEG + RBV [WBD]) to therapy with PEG + RBV (WBD) alone in previously untreated adult subjects with chronic hepatitis C (CHC) genotype 1. All subjects are to be randomized to 1 of 3 treatment arms. A description of each of these arms used in this protocol is presented below:

Control

<u>Arm 1:</u> PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by placebo + PEG 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

Experimental Therapy

<u>Arm 2</u>: PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 µg/kg + RBV (WBD) for 24 weeks.

At the Treatment Week (TW) 28 visit, subjects will be instructed by IVRS to follow one of the two options below based on their HCV-RNA results on and after TW 8.

a. At the TW 28 visit, subjects whose HCV-RNA was undetectable at TW 8 and at all subsequent assays will be instructed that they have completed their assigned treatment with boceprevir + PEG 1.5 µg/kg + RBV (WBD) and should proceed to 44 week follow-up. Sites and subjects will remain blinded as to their treatment arm until TW 28.

b. At the TW 28 visit, subjects with detectable HCV-RNA at TW 8 or at any subsequent assays will be instructed by IVRS to continue on therapy with PLACEBO + PEG 1.5 µg/kg + RBV (WBD) for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up. The switch from boceprevir to placebo will occur in a blinded fashion.

<u>Arm 3</u>: PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

Approximately 930 non-black/African American subjects (Cohort 1) are to be randomized to one of 3 treatment arms in a 1:1:1 ratio. Additionally, a separate cohort of at least 150 Black/African American (Cohort 2) subjects will also be enrolled in a 1:1:1 ratio. Within each cohort, randomized treatment assignment will be stratified based on baseline viral load: high viral load (>400,000 IU/mL) versus low viral load (≤400,000 IU/mL) based upon screening visit HCV-RNA result, and on HCV genotype 1a infection versus HCV genotype 1b infection. Those subjects with genotype 1 who cannot be classified as only 1a or 1b will be randomly assigned to a treatment arm within their HCV-RNA strata.

It is important to note that because there is a large difference between SVR rates for non-black patients and black patients (for traditional interferon-based therapies, as well as for boceprevir add-on therapy based on Phase II results), and because it is difficult to enroll reasonably large numbers of Black subjects in typical registration studies, this study was designed with two separate cohorts. Sample size calculations and formal statistical evaluations of the treatment differences are based on the non-black/African-American cohort of subjects because enrollment was expected to be predictable and completed within a reasonably accurate timeframe. The Black/African-American cohort was designed to continue enrollment until at least 150 subjects were randomized in order to provide more precise estimates

of the SVR rates and treatment differences than has been possible with typical registration studies. Descriptive statistics will be used to summarize the results for this cohort, and an overall test of SVR rates (combining results of cohort 1 and 2), controlling for cohorts, will also be provided for the primary and key secondary objectives

Because of the fundamental importance of race (non-Black vs. Black) on SVR rates and potentially on the corresponding treatment differences, it is both scientifically and statistically more appropriate to provide race-specific estimates of these quantities, rather than overall estimates based on a given study population (whose racial distribution may or may not be representative of any population of interest).

The data analysis plan (DAP) document is being finalized before the final analysis of the efficacy data. Assessments of the safety data were performed on June 11, 2009 and on December 03, 2009 by the DRAB (DRAB: Data Review Advisory Board, also referred to as DMC, Data Monitoring Committee). No efficacy evaluations were performed during these safety assessments.

2. HYPOTHESES / STUDY OBJECTIVES

2.1 Primary

The primary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg three times a day (TID) orally (PO) (hereafter called boceprevir) in combination with PegIntron 1.5 µg/kg weekly (QW) subcutaneously (SC) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO (hereafter called PEG + RBV [WBD]) to therapy with PEG + RBV (WBD) alone in previously untreated adult subjects with chronic hepatitis C (CHC) genotype 1. The primary objective will be statistically evaluated using data from all randomized subjects combining results from cohort 1 and 2. A separate analysis of cohort 1 (non black/African–American) will also be provided. . In addition, descriptive statistics on data from the all randomized black/African-American cohort of subjects will be provided.

Note that the primary objective of the study is to compare the two therapeutic regimens of boceprevir (in combination with PEG+RBV) with the control therapy (PEG+RBV) in the population defined by all randomized subjects. This was the primary objective stated in the original protocol, and it corresponds to providing treatment-specific estimates of SVR and estimates of the treatment differences for naïve, chronic hepatitis-C patients when they begin the treatment process (i.e., at the start of the lead-in period on PEG+RBV background therapy). However, another relevant and perhaps more meaningful estimate of the experimental treatment effect can be obtained from a population defined by those randomized subjects who were treated with at least one dose of the experimental study drug - boceprevir (for experimental arms) or placebo (for the control arm). In actual clinical practice, physicians will only add boceprevir to the treatment regimen of patients who successfully complete the lead-in period on background therapy; consequently, this population can be considered the "true" intent to treat population. In addition, because the study is blinded, there is no potential for introducing bias by excluding randomized subjects who did not receive at least one dose of experimental study drug (boceprevir or placebo). Estimates of the treatment differences based on this population are also statistically more precise because subjects who do not enter the experimental treatment period of the study can only add (random) noise to the estimates (if, by chance, there is an imbalance in the number of such subjects across the treatment arms). Finally, this approach is more consistent with the ultimate goal of using information obtained during the lead-in period (and the corresponding relationships to achieving SVR in the context of subsequent boceprevir treatment) to develop information and possibly recommendations that physicians can use to improve the benefit/risk ratio of boceprevir treatment for individual patients. For these reasons, the protocol was amended on December 02, 2009 to include the following KEY SECONDARY objective of the study. This key secondary objective differs from the primary objective in the definition of the population used to provide the treatment-specific estimates of SVR and estimates of the treatment differences.

2.2 Key Secondary

The key secondary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PEG+RBV (WBD) with the standard of care [PEG+RBV (WBD) alone] in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms). The key-secondary objective will be statistically evaluated using data from randomized subjects who received at least one dose of experimental study drug (boceprevir/placebo), combining results from cohort 1 and 2. A separate analysis of cohort 1 (non black/African-American) will also be provided. In addition, descriptive statistics on data from the black/African-American cohort of subjects who received at least one dose of experimental study drug (boceprevir/placebo) will be provided.

2.3 Secondary

Other secondary objectives of this study are:

- To evaluate the safety of boceprevir when used in combination with PEG + RBV (WBD).
- To identify predictors of sustained virologic response (SVR), such as epidemiologic factors, disease characteristics, and on-treatment response.
- To develop the relationship between steady-state pharmacokinetic parameters, obtained from population based pharmacokinetic model and responses in a subset of subjects.

3. POWER AND SAMPLE SIZE

This study is projected to enroll a total of 930 non-Black/African American subjects (310:310:310) in Arms 1, 2, and 3, respectively. With 310 subjects per arm, the study will have 90% power to detect a 13% improvement in the SVR rate, assuming a control SVR rate of 45% (i.e., 58% vs. 45%) using a 2-sided chi-square test at alpha=0.05.

Additionally, a minimum of 150 Black/African American subjects will be enrolled with no upper limit for enrollment. Enrollment for the first cohort (the cohort of non-Blacks/African Americans) will close when 930 non-Black/African American subjects are randomized, and enrollment for the second cohort (the cohort of Blacks/African Americans) will continue until at least 150 Black/African American subjects have been randomized. With 50 Black/African American subjects per arm, the true response rate in the Black/African American population can be estimated within ± 14% assuming an estimated response rate of 50% and using a 2-sided 95% confidence interval.

4. Study Endpoints

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of SVR, defined as undetectable plasma HCV-RNA at FW 24, in all randomized subjects (Full Analysis Set as defined in Sec 5.1) If a subject is missing FW 24 data and has undetectable HCV-RNA level at FW 12, the subject would be considered an SVR. More details on the derivation of the primary endpoint can be found in section 6.7.2.

4.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the achievement of` SVR, defined as undetectable plasma HCV-RNA at FW 24 in subjects who received at least one dose of the experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

4.3 Secondary Efficacy Endpoints

The secondary endpoints are:

- The proportion of subjects with early virologic response (egg, undetectable HCV-RNA at Treatment Weeks 2, 4, 8, 12)
- The proportion of subjects with early virologic response (egg, undetectable HCV-RNA at Treatment Weeks 2, 4, 8, 12) who achieved SVR
- The proportion of subjects with undetectable HCV-RNA at FW 12
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization

5. Datasets Analyzed

5.1 Full Analysis Set (FAS)

The Full Analysis Set will include all randomized subjects who receive at least one dose of any study medication (PEG or RBV or SCH 503034).

5.2 Modified Intent To Treat Data Set (MITT)

The modified intent to treat (MITT) data set will include all randomized subjects who receive at least one dose of experimental study drug - boceprevir (for the experimental therapy arms) or placebo (for the control arm). Subjects who discontinue during the 4 week lead-in period will not be included in the MITT set.

5.3 Per-Protocol Dataset

The "per protocol" dataset will include all subjects who meet *key protocol eligibility and evaluability criteria*. This dataset will be determined prior to the final clinical database lock. The key eligibility and evaluability criteria will be documented in the data management plan.

Separate statistical analyses will be conducted for the cohort of non-Blacks/African Americans and for the cohort of Blacks/African American subjects, and the results will be presented for each cohort separately. In addition, an overall analysis which combines the results from cohort 1 and cohort 2 will be provided.
For all efficacy analyses, patients will be included in the treatment arm to which they are randomized. For all safety analyses, subjects will be included in the treatment arm corresponding to the study treatment they actually received.

6. Statistical Methods

6.1 Primary Efficacy Analysis

The primary efficacy analysis will be carried out to evaluate the primary objective of the trial, and will be based on the FAS (all randomized subjects who receive at least one dose of any study medication [PegIntron, Ribavirin, or Boceprevir/Placebo]). The primary efficacy endpoint, the achievement of SVR,

will be summarized using descriptive statistics (n, %) for each of the three treatment arms and will be presented separately for the non Black/AA and Black/AA cohorts. Statistical comparisons among the treatment arms within each cohort will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (controlling for the baseline stratification factors). Since there are only 50 subjects to be randomized per arm in the black/AA cohort of the study, the treatment comparisons in this cohort may not be adequately powered.

Additionally, stratum-adjusted treatment differences and their adjusted 95% Confidence Intervals based on an overall analysis that combines results from cohort 1 and cohort 2 will also be provided (adjusted for both race and baseline stratification factors). Computation of stratum-adjusted differences and their confidence intervals will be based on methodology defined in Koch et al[1] . Overall P-values will be computed based on the two-sided Cochran-Mantel Haenszel (CMH) chi-square test controlling for the race cohorts as well as the baseline stratification factors.

[1] Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), **Statistical Methodology in the Pharmaceutical Sciences**, Marcel Dekker, New York, pp. 414-421

6.2 Key Secondary Efficacy Analysis

The key secondary efficacy analysis will be carried out to evaluate the key secondary objective of the trial, and will be based on the MITT data set (all randomized subjects who receive at least one dose of boceprevir for the experimental therapy arms or placebo for the control arm). The SVR rate will be summarized using descriptive statistics (n, %) for each of the three treatment arms in the MITT data set. and will be presented separately for the non black/AA and black/AA cohorts. Statistical comparisons for the key secondary efficacy analysis will be carried out within each race cohort using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (controlling for the baseline stratification factors).

Additionally, stratum-adjusted treatment differences and their adjusted 95% Confidence Intervals based on an overall analysis that combined results from cohort 1 and cohort 2 will also be provided adjusted for both race and baseline stratification factors. Computation of stratum-adjusted differences and their confidence intervals will be based on methodology defined in Koch et al [1]. Overall P-values will be computed based on the two-sided Cochran-Mantel Haenszel (CMH) chi-square test controlling for the race cohorts as well as the baseline stratification factors.

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Multiplicity adjustments for primary and key secondary comparisons are discussed in detail in section 6.8.

6.3 Secondary Efficacy Analyses

Virologic response rates at various time points during treatment (TW 2, TW4, TW8, TW12, TW20, TW24, TW28, TW48, EOT) as well as during follow up (FW 12, FW24 and at 72 weeks post randomization) will be summarized using descriptive statistics (n, %) for the three treatment arms.

The relationship between early virologic response (such as: virologic response at TW2, TW4 etc.) and SVR will be summarized using the proportion of subjects who achieve SVR among subjects with undetectable HCV-RNA at TWs 2, 4, 8, or 12. The concordance between virologic response at FW 12 and 72 weeks post-randomization to SVR will be assessed by tabulating the proportion of subjects with undetectable HCV-RNA at these time points (FW 12 and 72 weeks post randomization) who also achieve SVR.

The effect of interferon (PEG + RBV) response during the first 4 weeks of lead in on the SVR rate will be assessed by summarizing the change from baseline in the log10 viral load at TW 4 (e.g., categorized as <1 log10-drop, 1-5 log10-drop, etc) and the SVR rate for

subjects in these various categories.

A logistic regression analysis with SVR as the dependent variable will be fit using treatment assignment, stratification factors, baseline disease characteristics defined in Sec 6.6 (Subgroup Analysis), and other known prognostic factors as independent variables, to identify predictors of response. Logistic regression analyses will also be conducted within each treatment arm. Both univariate and multivariable models (full model and stepwise selection method) will be used to make these evaluations.

A separate model that evaluates the on-treatment response (log viral load drop and response status at TW 4, TW8, TW 12, and time to first negativity) in addition to baseline factors will also be conducted to assess the impact of early response on SVR.

All secondary and exploratory analyses will be performed on the non-Black/African American cohort. Results from the Black/African American cohort of the study will be summarized separately, and if there is adequate data for the black/AA cohort, then secondary and exploratory analyses may be also be performed separately on this cohort.

6.4 Additional Efficacy Analyses

To assess the effect of the different boceprevir treatment regimens on the primary efficacy outcome, two-sided 95% confidence interval for the difference in SVR (obtained using Normal approximation for binary data) will be used for:

- Comparing Boceprevir treatment strategies: Arm 2 vs. Arm 3;
- Comparison of 28 weeks vs. 48 weeks of treatment in subjects who achieved early virologic response: Subjects in Arm 2 with undetectable HCV-RNA at TW 8 and at all subsequent assays up to TW 28 who were assigned to short term treatment (28 weeks, Arm 2a) vs. subjects in Arm 3 with undetectable HCV-RNA at TW 8 and at all subsequent assays up to TW 28;
- PEG/RBV/BOC vs. PEG/RBV during the last 20 weeks of treatment in subjects who did not achieve early virologic response: Comparing Subjects in Arm 2 with detectable HCV-RNA at TW 8 or at any subsequent assays up to TW 28 who were assigned additional 20 weeks of PEG/RBV/Placebo (Arm 2b) vs. subjects in Arm 3 with detectable HCV-RNA at TW 8 or at any subsequent assays up to TW 28.
    - In addition, subjects who were HCV-RNA undetectable at TW 8 but were detectable at any subsequent assays up to TW 28 will be excluded from Arm 2b for the analysis, compared to subjects in Arm 3 who were HCV-RNA detectable at TW 8.

Other Exploratory Analyses

Genetic classification (such as IL28) of subjects may be evaluated as a predictor of the sustained virologic response by frequency tables and logistic regression models. Interferon response gene data may be evaluated to identify the association with viral response.

An exploratory analysis using logistic regression model will be conducted to identify characteristics of subjects for whom shorter duration of therapy may be adequate. Baseline characteristics as well as on-treatment factors (Baseline viral load, log viral drop and response status at TW4, TW8 etc.) will be considered for this.

6.5 Supportive Analyses

As part of sensitivity analyses, primary, key secondary and secondary efficacy analyses will also be repeated on the Per-Protocol data set. Proportion of subjects who relapse will be summarized by treatment group. Relapse is defined as having an undetectable HCV-RNA at EOT and a detectable HCV-RNA at end of follow-up week 24. The relapse rate will be calculated among subjects who have data at end of treatment and end of follow-up.

In addition, rate of viral breakthrough and incomplete viral response (IVR) will be summarized by treatment group using descriptive statistics.

Analyses to assess the effect of treatment adherence/compliance on sustained response rates will be performed. This will include summarizing SVR rates by treatment arms for subjects who took at least 80% of the assigned study medications (for pegylated interferon, ribavirin and boceprevir) for 80% of the study duration. Different completers analyses (e.g. completers defined as subjects who completed at least 80% of the study) will also be performed. Adherence for boceprevir dosing amount alone as well as dosing interval (7-9 hours) for boceprevir may be evaluated to assess the effect on sustained virologic response.

6.5.1 Evaluation of Anemia & Use of EPO effect on response

In this study, majority of the subjects who became anemic during treatment are expected to use EPO. Proportion of subjects who become anemic during treatment (defined as minimum HGB <10 g/dl) and proportion of subjects who used EPO during treatment will be summarized by treatment arm. Duration and the weekly EPO dose will be summarized by treatment arm using mean, median, std, min and max. Changes in Hemoglobin (g/dl) levels after EPO start will be tabulated by treatment arm (mean, median, std, min, max).

Virologic response (EOT, SVR) by anemia status (yes, no) will be summarized as proportions for each of the treatment arms. Time of onset of anemia will be calculated and summarized as categories based on weeks: 0-4 weeks, >4 – 8 weeks, etc. as well as Early vs. Late for the treatment arms. Virologic response rates for these time categories will be presented. Relation of response and time of anemia will also be explored using logistic regression models as well as classification tree based methods.

To evaluate the impact of EPO use on response, proportion of subjects who achieve response (undetectable HCV-RNA) at various time points (EOT, SVR) by EPO users and non-users will be summarized for each treatment arm. Response by EPO users (and non-users) will also be tabulated for subjects who become anemic (minimum hemoglobin <10 g/dL) during treatment vs. those who do not. Relapse rates among EPO vs. No EPO groups will be summarized for each treatment arm.

To analyze the effect of EPO on subject discontinuation rate, proportion of subjects who discontinue treatment by EPO users vs. non-users will be summarized by treatment arm. Time adjusted discontinuation rates will also be evaluated for EPO vs. no EPO groups. For example, proportion of subjects who had EPO vs. no EPO among the subjects who discontinued by TW12 (and other time points) will be summarized by treatment arm. For subjects who received EPO, Kaplan-Meier estimates for time to discontinuation and time to adverse event since EPO begin date will be computed by treatment arm.

6.5.2 Sustained Response by PK Parameters

(See section 8.7.3 of protocol): In order to evaluate the relationship between SCH503034 PK parameters (AUC, Cmax, Cmin) with virologic response, the proportion of subjects who respond (HCV-RNA undetectable) at EOT and FU 24 (SVR) will be tabulated for each of the four quartiles based on the PK parameters. Log viral drop from baseline may also be summarized (mean, median, std, min, max) by the four quartiles of each of the PK parameters. PK/PD relationship will be further explored using graphical techniques and logistic / linear regression modeling.

6.6 Subgroup Analysis

SVR rates and two-sided 95% confidence intervals by treatment arm will be provided for the subgroups based on baseline demographic and baseline disease characteristic and stratification factors. SVR rates for subgroups will be presented separately for the cohort of non-Blacks/African Americans and for the cohort of Blacks/African Americans.

Baseline factors to be examined will include:

- Race :

- White, non-White

- Baseline HCV-RNA :
  - ≤400,000 IU/ml, >400,000 IU/ml
- Gender : M/F
- Age Group: <=40 yrs, > 40 yrs, and in 10 year increments
- Weight :
  - 40-50 kg, >50 – 65 kg, >65 – 80 kg, >80-105 kg, >105 – 125 kg
  - < 75 kg vs. >=75 kg
- BMI: <=20, > 20 -25, >25-30, > 30
- Baseline Platelets:
  - <100,000/µl
  - 100,000-150,000/µl
  - 150,000-200,000/µl
  - >200,000/µl
- Metavir fibrosis Score: F0, 1, 2, 3, 4 and F 0/1/2 vs. F 3/4
- Steatosis: 0%, >0-5%. >5 – 32%. >32 – 66%, > 66%
- Liver Cirrhosis: Cirrhosis vs. no Cirrhosis
- Genotype :
  - 1A, 1B based on VIRCO reported data
  - 1A, 1B based on COVANCE reported data
- Subjects receiving EPO (Yes/No)
- ALT (elevated vs. normal at baseline)
- Use of Statins (Yes/No)

6.7 Procedures for Handling of Data

6.7.1 Genotype Data

For all secondary and exploratory analyses, genotype classification based on VIRCO reported data will be used instead of the COVANCE reported data. An evaluation of concordance between VIRCO and COVANCE data will be conducted.

6.7.2 Missing Data

During the treatment period, any subject missing an HCV-RNA evaluation at any particular visit window will be considered to be a non-responder for that visit.

If there is a missing value for FW 24 window, then the closest value after this window will be considered to be the FW 24 value (next value carried backwards – NVCB). If there are no values within or

after the FW 24 week window but values have been assigned to the FW 12 window, then the FW 12 week values will be assigned to FW 24 (FW12 carried forward).

In addition, the following approach for imputing missing data will also be considered. If after NVCB there are still missing values in the FW24 window, these will be considered as non-responders (missing = failure).

Other sensitivity analyses to assess the impact of missing data may be performed if a sufficient number of subjects are missing follow-up week 24 data but were known to have completed the treatment. These analyses may include using the relapse rates to impute the missing follow-up virology data for subjects who are HCV-RNA negative at the end of treatment but are missing follow-up 24 data (relapse rate is defined as the proportion of patients that have a detectable HCV-RNA level at follow-up week 24 given that they have an undetectable HCV-RNA level at the end of treatment).

6.8 Multiplicity Adjustments

In order to control the type 1 error for the two comparisons (Arm 3 vs. Control, and Arm 2 vs. Control) for the primary efficacy analysis, a step down approach will be carried out for hypothesis testing. First, the 48 week experimental group (Arm 3) will be compared against the control arm using the 2-sided CMH chi-square test, controlling for the baseline stratification factors. If the p-value is less than 0.05, efficacy of 48 weeks of treatment with boceprevir over the pegintron/ribavirin control group will be established and the next comparison will be carried out, i.e., the 28/48 week experimental group (Arm 2) will be compared against the control arm using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28/48 week arm will also be established.

To account for the multiplicity between the primary and key-secondary analyses, we will step down to the key-secondary analyses if the significance of the primary comparisons has been established.

A step down approach will be used to control the type 1 error for the two key-secondary comparisons. First, the 48 week experimental group (Arm 3 for subjects who have received at least one dose of boceprevir) will be compared against the control arm (for subjects who received at least one dose of placebo) using the two-sided CMH chi-square test, controlling for the baseline stratification factors. If this p-value is less than 0.05, the next comparison will be carried out, i.e., the 28/48 week experimental group (Arm 2 for subjects who received at least one dose of boceprevir) will be compared against the control arm (for subjects who received at least one dose of placebo) using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28/48 week arm will also be established.

7. Interim Analyses

No interim analyses of the efficacy data are planned. Safety data will be reviewed by the DRAB on an ongoing basis.

8. Safety Analyses

The safety analyses will be based on the FAS data set. For all safety analyses, subjects will be analyzed as treated. No inferential statistical analyses are planned. All safety summaries and tabulations will be presented by treatment group. In order to get a safety perspective of subjects after the boceprevir start date, tables will also be generated for the post lead-in period.

The number of subjects reporting any AEs and the incidence of specific AEs and SAEs will be tabulated. The proportion of subjects with discontinuation due to AEs or dose modification due to AEs will be summarized. The number of subjects with AEs and number of discontinuations that begin after the initiation of triple therapy (the arms with 4 weeks of PegIntron/ribavirin lead in) will also be summarized.

Laboratory parameters hemoglobin, WBC, neutrophils, platelets, creatinine, AST and ALT will be tabulated using protocol defined modified WHO criteria. For these same laboratory parameters, the number of subjects meeting protocol specified values for either dose reduction or dose discontinuation will be

summarized. Laboratory data will also be listed by the treatment group and values outside the normal range will be flagged.

Vital signs (pulse, weight, etc) will be summarized. Also, the proportion of subjects requiring the use of hematopoietic growth factors will be tabulated.

9. Derived Visit Window Conventions

A detailed description of the data derivation rules can be found in the dataset specification file. The main conventions for the visit window definitions appear below.

Baseline Period: Period on or before the randomization date.
Treatment Begin Date: Earliest of any study drug begin date (PEG/RBV/Blinded drug)

Treatment Period: Period after treatment begin date to treatment stop date plus 7 days, inclusive.

Follow-up Period: Period beginning after treatment stop date plus 7 days.

Virology Windows and Conventions for Virology Data:

If two or more valid virology values are associated with the same collection date, pick the worst value (highest HCV-RNA viral load) to be the derived value.

Baseline:

The baseline value will be expressed as a geometric mean of all the HCV-RNA values from samples drawn on or before the randomization date and assayed by Covance laboratories. If there is a '<25 IU/mL' HCV-RNA value on or before the randomization date and there are other repeat labs within the baseline period, the <25 IU/mL value will be excluded from the geometric mean calculation as this is likely a mislabeled sample.

SUPPLEMENTARY APPENDIX III

[Additional Tables and Figures]

for

Boceprevir with Peginterferon and Ribavirin

For Chronic Hepatitis C

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Table S1. Baseline Characteristics of Randomized Patients Treated with One or More Doses of Any Study Medication

	Cohort 1 (Non-black patients)			Cohort 2 (Black patients)			Combined Cohorts (All patients)		
	Arm 1 (PR48)	**Arm 2 (BOC RGT†)**	**Arm 3 (BOC/ PR48†)**	**Arm 1 (PR48)**	**Arm 2 (BOC RGT†)**	**Arm 3 (BOC/ PR48†)**	**Arm 1 (PR48)**	**Arm 2 (BOC RGT†)**	**Arm 3 (BOC/ PR48†)**
	N = 311	N = 316	N = 311	N = 52	N = 52	N = 55	N = 363	N =368	N =366
Mean age, years (SD)	48 (10)	49 (9)	49 (9)	51 (9)	52 (8)	51 (7)	49 (10)	50 (9)	49 (9)
Gender, n (%)									
Male	171 (55)	200 (63)	188 (60)	35 (67)	29 (56)	33 (60)	206 (57)	229 (62)	221 (60)
Female	140 (45)	116 (37)	123 (40)	17 (33)	23 (44)	22 (40)	157 (43)	139 (38)	145 (40)
Self-identified Race¶, n (%)									
White	296 (95)	304 (96)	295 (95)	--	--	--	296 (82)	304 (83)	295 (81)
Black	--	--	--	52 (100)	52 (100)	55 (100)	52 (14)	52 (14)	55 (15)
Asian	9 (3)	4 (1)	8 (3)	--	--	--	9 (2)	4 (1)	8 (1)
Other (including multi-racial)	6 (2)	8 (3)	8 (3)	--	--	--	6 (2)	8 (2)	8 (2)
Region, n (%)									
North America	203 (65)	226 (72)	218 (70)	51 (98)	51 (98)	52 (95)	254 (70)	277 (75)	270 (74)
Europe	98 (32)	78 (25)	83 (27)	1 (2)	1 (2)	3 (5)	99 (27)	79 (21)	86 (23)
Latin America	10 (3)	12 (4)	10 (3)	0 (0)	0 (0)	0 (0)	10 (3)	12 (3)	10 (3)
Mean Weight, kg (SD)	79 (16)	82 (17)	80 (17)	87 (14)	86 (15)	91 (18)	80 (16)	82 (17)	82 (17)
Mean BMI, kg/M^2 (SD)	27 (5)	28 (5)	27 (5)	29 (4)	29 (5)	31 (6)	27 (5)	28 (5)	28 (6)
HCV genotype, n (%)									
Subtype by TRUGENE assay									

1a	144 (46)	144 (46)	153 (49)	33 (63)	35 (67)	34 (62)	177 (49)	179 (49)	187 (51)
1b	114 (37)	120 (38)	117 (38)	12 (23)	14 (27)	16 (29)	126 (35)	134 (36)	133 (36)
indeterminate	53 (17)	52 (16)	41 (13)	7 (13)	3 (6)	5 (9)	60 (17)	55 (15)	46 (13)
Subtype by VIRCO assay									
1a	186 (60)	195 (62)	197 (63)	41 (79)	39 (75)	40 (73)	227 (63)	234 (64)	237 (65)
1b	112 (36)	111 (35)	104 (33)	9 (17)	13 (25)	13 (24)	121 (33)	124 (34)	117 (32)
non-1	2 (1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (<1)	1 (<1)
indeterminate	11 (4)	9 (3)	9 (3)	2 (4)	0 (0)	2 (4)	13 (4)	9 (2)	11 (3)
HCV RNA level, n (%)									
Geometric mean, log IU/mL	6.5	6.5	6.5	6.7	6.5	6.7	6.5	6.5	6.5
>400,000 IU/mL	285 (92)	287 (91)	288 (93)	52 (100)	49 (94)	53 (96)	337 (93)	336 (91)	341 (93)
>800,000 IU/mL	258 (83)	268 (85)	262 (84)	50 (96)	46 (88)	51 (93)	308 (85)	314 (85)	313 (86)
ALT > upper limit of normal range, n (%)	233 (75)	252 (80)	247 (79)	36 (69)	41 (79)	34 (62)	269 (74)	293 (80)	281 (77)
Baseline platelet count, n (%)									
<150,000 per µL	25 (8)	30 (9)	34 (11)	2 (4)	3 (6)	4 (7)	27 (7)	33 (9)	38 (10)
≥150,000 per µL	286 (92)	286 (91)	277 (89)	50 (96)	49 (94)	51 (93)	336 (93)	335 (91)	328 (90)
Statin use, n (%)									
Yes	2 (1)	8 (3)	3 (1)	1 (2)	1 (2)	4 (7)	3 (1)	9 (2)	7 (2)
No	309 (99)	308 (97)	308 (99)	51 (98)	51 (98)	51 (93)	360 (99)	359 (98)	359 (98)
METAVIR score[§], n (%)									
F0	16 (5)	17 (5)	9 (3)	1 (2)	3 (6)	1 (2)	17 (5)	20 (5)	10 (3)
F1	206 (66)	212 (67)	208 (67)	40 (77)	26 (50)	38 (69)	246 (68)	238 (65)	246 (67)
F2	55 (18)	50 (16)	48 (15)	10 (19)	11 (21)	9 (16)	65 (18)	61 (17)	57 (16)
F3 (bridging fibrosis)	10 (3)	13 (4)	14 (5)	1 (2)	5 (10)	4 (7)	11 (3)	18 (5)	18 (5)
F4 (cirrhosis)	13 (4)	13 (4)	22 (7)	0 (0)	3 (6)	2 (4)	13 (4)	16 (4)	24 (7)

F0, F1 or F2	277 (89)	279 (88)	265 (85)	51 (98)	40 (77)	48 (87)	328 (90)	319 (87)	313 (86)
F3 or F4	23 (7)	26 (8)	36 (12)	1 (2)	8 (15)	6 (11)	24 (7)	34 (9)	42 (11)
Missing or inadequate	11 (4)	11 (3)	10 (3)	0 (0)	4 (8)	1 (2)	11 (3)	15 (4)	11 (3)
Steatosis[§], n (%)									
Absent	108 (35)	92 (29)	93 (30)	20 (38)	15 (29)	15 (27)	128 (35)	107 (29)	108 (30)
Present	192 (62)	213 (67)	208 (67)	32 (62)	33 (63)	39 (71)	224 (62)	246 (67)	247 (67)
Missing or inadequate	11 (4)	11 (3)	10 (3)	0 (0)	4 (8)	1 (2)	11 (3)	15 (4)	11 (3)

PR, peginterferon/ribavirin; BOC, boceprevir; SD, standard deviation.

[†] Boceprevir was to be given for 24 weeks in Arm 2 (irrespective of the rapidity of virologic response) and for 44 weeks in Arm 3.

[¶] In Cohort 1, 8%-13% of patients in each treatment arm described their ethnicity as Hispanic or Latino; all but 1 of these patients were in Cohort 1.

[§] METAVIR scores were based on the review and interpretation of the liver biopsy by a single blinded pathologist.

Table S2A. Types and Frequencies of Treatment-Emergent[§] Adverse Events (AE) in the Combined Cohorts

	Arm 1 (PR48)	**Arm 2 (BOC RGT)**	**Arm 3 (BOC/PR48)**
	N = 363	N = 368	N = 366
Mean (Median) Duration of Treatment, days	236 (203)	200 (197)	261 (335)
Number (%) of Patients			
with one or more AE	356 (98)	365 (99)	364 (99)
with serious AE (including death)	31 (9)	42 (11)	45 (12)
with adverse event leading to dose modification	94 (26)	146 (40)	129 (35)
with life-threatening AE	4 (1)	5 (1)	4 (1)
who died	4 (1)	1 (<1)	1 (<1)
who discontinued due to AE	57 (16)	45 (12)	60 (16)

PR, peginterferon/ribavirin; BOC, boceprevir.
[§] Includes all specified adverse events occurring on study treatment or within 30 days of its discontinuation, regardless of causality.

Table S2B. Common Treatment-Emergent Clinical Adverse Events[†], Resistance-Associated HCV Variants, and Specific Hematologic Laboratory Abnormalities in the Combined Cohorts

	Arm 1 (PR48)	Arm 2 (BOC RGT)	p-value[*] Arm 2 *vs.* Arm 1	Arm 3 (BOC/PR48)	p-value[*] Arm 3 *vs.* Arm 1
	N = 363	N = 368		N = 366	
Investigator-reported clinical adverse events, n (%)					
Fatigue	217 (60)	196 (53)	0.09	209 (57)	0.50
Headache	153 (42)	168 (46)	0.37	167 (46)	0.37
Nausea	153 (42)	175 (48)	0.16	159 (43)	0.76
Anaemia	107 (29)	182 (49)	<0.001	179 (49)	<0.001
Pyrexia	121 (33)	123 (33)	0.99	118 (32)	0.81
Chills	102 (28)	134 (36)	0.02	121 (33)	0.15
Dysgeusia	64 (18)	137 (37)	<0.001	156 (43)	<0.001
Insomnia	118 (33)	117 (32)	0.87	122 (33)	0.81
Pruritus	98 (27)	87 (24)	0.31	94 (26)	0.74
Alopecia	99 (27)	75 (20)	0.03	104 (28)	0.74
Decreased appetite	90 (25)	97 (26)	0.67	89 (24)	0.93
Influenza-like illness	93 (26)	91 (25)	0.80	83 (23)	0.39
Myalgia	94 (26)	78 (21)	0.14	92 (25)	0.87
Rash	83 (23)	93 (25)	0.49	88 (24)	0.73
Neutropenia	77 (21)	92 (25)	0.25	93 (25)	0.19
Diarrhoea	79 (22)	80 (22)	0.99	100 (27)	0.09
Irritability	86 (24)	81 (22)	0.60	83 (23)	0.79
Depression	79 (22)	83 (23)	0.86	69 (19)	0.36
Dry skin	66 (18)	67 (18)	0.99	86 (23)	0.08
Dyspnoea	59 (16)	68 (18)	0.44	84 (23)	0.03
Arthralgia	66 (18)	69 (19)	0.85	72 (20)	0.64
Dizziness	60 (17)	80 (22)	0.08	67 (18)	0.56
Cough	76 (21)	56 (15)	0.05	74 (20)	0.85

Vomiting	57 (16)	75 (20)	0.10	72 (20)	0.17
Asthenia	70 (19)	55 (15)	0.14	70 (19)	0.99
Boceprevir Resistance-Associated Variants, n/m (%)[¶]					
Overall	N/A	59/350 (17)	N/A	52/354 (15)	N/A
Week 4 decline in HCV RNA from baseline					
Undetectable	N/A	0/19 (0)	N/A	0/20 (0)	N/A
≥1 log decline	N/A	10/232 (4)	N/A	13/231 (6)	N/A
<1 log decline (poorly responsive to IFN)	N/A	49/95 (52)	N/A	38/94 (40)	N/A
Missing	N/A	0/4 (0)	N/A	1/9 (11)	N/A
Hematological parameters, n (%)					
Decreased absolute neutrophil count					
Toxicity grade, n (%)					
Grade 0 (>1500/µL)	83 (23)	52 (14)	0.003	56 (15)	0.01
Grade 1 (1000 to ≤1500/µL)	125 (35)	105 (29)	0.09	92 (25)	0.007
Grade 2 (750 to <1000/µL)	84 (23)	98 (27)	0.30	98 (27)	0.27
Grade 3 (500 to <750/µL)	50 (14)	87 (24)	<0.001	90 (25)	<0.001
Grade 4 (<500/µL)	16 (4)	21 (6)	0.50	29 (8)	0.06
Use of granulocyte-stimulating agent, n (%)	21 (6)	43 (12)	0.006	31 (8)	0.20
Decreased platelet count					
Toxicity grade, n (%)					
Grade 0 (>100,000/µL)	308 (87)	262 (72)	<0.001	243 (67)	<0.001
Grade 1 (70,000 to ≤100,000/µL)	38 (11)	63 (17)	0.01	72 (20)	<0.001
Grade 2 (50,000 to <70,000/µL)	4 (1)	26 (7)	<0.001	36 (10)	<0.001
Grade 3 (25,000 to <50,000/µL)	5 (1)	11 (3)	0.21	13 (4)	0.09
Grade 4 (<25,000/µL)	0 (0)	1 (<1)	0.99	1 (<1)	0.99
Decreased hemoglobin concentration					
Mean change [g/dL] from baseline					
Week 12	-3.0	-4.0	<0.001	-3.9	<0.001
Week 24	-3.1	-4.1	<0.001	-3.9	<0.001

Week 48	-3.2	-3.4	0.37	-3.9	<0.001
Toxicity grade[§], n (%)					
Grade 0 (≥11 g/dL)	161 (45)	88 (24)	<0.001	83 (23	<0.001
Grade 1 (9.5 to <11 g/dL)	130 (36)	161 (44)	0.03	152 (42)	0.13
Grade 2 (8.0 to <9.5 g/dL)	61 (17)	105 (29)	<0.001	117 (32)	<0.001
Grade 3 (6.5 to <8.0 g/dL)	6 (2)	7 (2)	0.99	12 (3)	0.23
Grade 4 (<6.5 g/dL)	0 (0)	2 (1)	0.50	1 (<1)	0.99
Red blood cell transfusion, n (%)	2 (1)	11 (3)	0.02	9 (2)	0.06
Use of erythropoietin, n (%)	87 (24)	159 (43)	<0.001	159 (43)	<0.001
Mean (median) duration of use[‡], days	121 (109)	94 (85)	0.01	156 (149)	0.005

IFN, interferon.

[†] Includes all specified adverse events occurring on study treatment or within 30 days of its discontinuation, regardless of causality, reported in ≥15% of patients in any treatment arm. Terms are from MedRA version 13.0, and listed by decreasing overall frequency.

[*] Nominal p-values are based on Fisher's exact test for categorical variables and t-test for continuous variables, and not corrected for multiplicity.

[¶] n/m indicates the number of patients with boceprevir resistance-associated variants out of the number of patients tested in the specified category.

[§] Modified WHO grade based on nadir hemoglobin level on treatment.

[‡] Calculated for patients who received erythropoietin.

Table S2C. All Serious Treatment-Emergent Clinical Adverse Events[§] Regardless of Frequency or Causality in the Combined Cohorts

	Control		Experimental			
	Arm 1[†] PR48 N=363		Arm 2[††] RGT N=368		Arm 3[†††] BOC/PR48 N=366	
	Number (%) of Subjects					
Subjects Reporting Any Serious Adverse Event	31	(9)	42	(11)	45	(12)
Blood and Lymphatic System Disorders	2	(1)	4	(1)	5	(1)
Anaemia	1	(<1)	3	(1)	4	(1)
Aplasia Pure Red Cell	0		0		1	(<1)
Leukocytosis	1	(<1)	0		0	
Leukopenia	0		0		2	(1)
Neutropenia	0		1	(<1)	2	(1)
Pancytopenia	0		0		1	(<1)
Thrombocytopenia	0		0		3	(1)
Cardiac Disorders	2	(1)	5	(1)	2	(1)
Acute Myocardial Infarction	0		1	(<1)	0	
Atrial Fibrillation	0		1	(<1)	0	
Atrial Flutter	0		1	(<1)	0	
Cardiac Arrest	1	(<1)	0		1	(<1)
Cardio-Respiratory Arrest	1	(<1)	0		0	
Coronary Artery Disease	0		1	(<1)	0	
Coronary Artery Occlusion	0		1	(<1)	0	
Hypertrophic Cardiomyopathy	0		1	(<1)	0	
Myocardial Infarction	1	(<1)	0		0	
Tachycardia	0		0		1	(<1)
Ear and Labyrinth Disorders	0		0		1	(<1)
Deafness	0		0		1	(<1)
Endocrine Disorders	1	(<1)	0		0	
Hypothyroidism	1	(<1)	0		0	
Eye Disorders	0		1	(<1)	2	(1)
Conjunctivitis	0		0		1	(<1)
Optic Neuropathy	0		0		1	(<1)
Papilloedema	0		1	(<1)	0	
Gastrointestinal Disorders	5	(1)	4	(1)	6	(2)

	Control	Experimental	
	Arm 1† PR48 N=363	Arm 2†† RGT N=368	Arm 3††† BOC/PR48 N=366
Abdominal Pain	1 (<1)	1 (<1)	1 (<1)
Abdominal Pain Lower	0	0	1 (<1)
Colitis	1 (<1)	0	0
Colonic Polyp	0	0	1 (<1)
Gastritis	0	0	1 (<1)
Gastrointestinal Haemorrhage	0	1 (<1)	0
Gastrooesophageal Reflux Disease	0	1 (<1)	0
Haematemesis	0	1 (<1)	0
Haemorrhoidal Haemorrhage	0	0	1 (<1)
Haemorrhoids	0	0	1 (<1)
Mallory-Weiss Syndrome	0	1 (<1)	0
Nausea	1 (<1)	0	1 (<1)
Pancreatitis	2 (1)	0	0
Pancreatitis Acute	0	0	1 (<1)
Umbilical Hernia	0	1 (<1)	0
Vomiting	1 (<1)	0	2 (1)
General Disorders and Administration Site Conditions	4 (1)	3 (1)	9 (2)
Chest Discomfort	0	0	2 (1)
Chest Pain	0	1 (<1)	4 (1)
Death	2 (1)	0	0
Fatigue	0	0	1 (<1)
General Physical Health Deterioration	0	0	1 (<1)
Malaise	0	1 (<1)	0
Pyrexia	2 (1)	1 (<1)	3 (1)
Hepatobiliary Disorders	3 (1)	0	1 (<1)
Cholecystitis	1 (<1)	0	1 (<1)
Cholecystitis Acute	1 (<1)	0	0
Cholelithiasis	2 (1)	0	0
Cholelithiasis Obstructive	1 (<1)	0	0
Immune System Disorders	0	0	1 (<1)
Sarcoidosis	0	0	1 (<1)
Infections and Infestations	7 (2)	12 (3)	8 (2)
Abscess	0	1 (<1)	0

	Control	Experimental	
	Arm 1† PR48 N=363	Arm 2†† RGT N=368	Arm 3††† BOC/PR48 N=366
Abscess Limb	0	0	1 (<1)
Appendicitis	1 (<1)	0	0
Atypical Mycobacterial Infection	1 (<1)	0	0
Bacteraemia	0	0	1 (<1)
Bronchitis	0	2 (1)	0
Cellulitis	1 (<1)	1 (<1)	2 (1)
Diverticulitis	1 (<1)	0	0
Enterocolitis Infectious	1 (<1)	0	0
Epiglottitis	0	1 (<1)	0
Gastroenteritis	0	2 (1)	2 (1)
Infected Bites	0	1 (<1)	0
Injection Site Infection	0	0	1 (<1)
Perirectal Abscess	0	1 (<1)	0
Pneumonia	1 (<1)	3 (1)	1 (<1)
Pneumonia Pneumococcal	0	0	1 (<1)
Scrotal Abscess	0	0	1 (<1)
Sinusitis	1 (<1)	0	0
Staphylococcal Infection	0	0	1 (<1)
Tracheobronchitis	0	0	1 (<1)
Upper Respiratory Tract Infection	1 (<1)	0	0
Injury, Poisoning and Procedural Complications	2 (1)	2 (1)	4 (1)
Accidental Overdose	1 (<1)	0	0
Alcohol Poisoning	1 (<1)	0	0
Overdose	0	0	1 (<1)
Post Procedural Complication	0	1 (<1)	0
Road Traffic Accident	0	0	1 (<1)
Spinal Fracture	1 (<1)	0	0
Transfusion Reaction	0	0	1 (<1)
Vascular Pseudoaneurysm	0	1 (<1)	0
Wound Dehiscence	0	0	1 (<1)
Investigations	1 (<1)	0	0
White Blood Cell Count Decreased	1 (<1)	0	0
Metabolism and Nutrition Disorders	0	2 (1)	1 (<1)

	Control	Experimental	
	Arm 1† PR48 N=363	Arm 2†† RGT N=368	Arm 3††† BOC/PR48 N=366
Dehydration	0	0	1 (<1)
Hypokalaemia	0	2 (1)	0
Hyponatraemia	0	1 (<1)	0
Musculoskeletal and Connective Tissue Disorders	0	2 (1)	2 (1)
Back Pain	0	0	1 (<1)
Flank Pain	0	1 (<1)	0
Groin Pain	0	0	1 (<1)
Intervertebral Disc Protrusion	0	1 (<1)	0
Musculoskeletal Chest Pain	0	0	1 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	4 (1)	3 (1)	2 (1)
Bladder Cancer	0	0	1 (<1)
Breast Cancer	1 (<1)	0	1 (<1)
Colon Cancer	0	1 (<1)	0
Hepatic Neoplasm Malignant	1 (<1)	0	0
Lung Adenocarcinoma	1 (<1)	0	0
Pancreatic Carcinoma	0	1 (<1)	0
Prostate Cancer	1 (<1)	1 (<1)	0
Nervous System Disorders	2 (1)	4 (1)	5 (1)
Carotid Artery Stenosis	0	1 (<1)	0
Cerebral Ischaemia	0	1 (<1)	0
Dizziness	1 (<1)	0	1 (<1)
Hypoaesthesia	1 (<1)	0	0
Loss Of Consciousness	1 (<1)	0	0
Motor Neurone Disease	0	1 (<1)	0
Muscle Spasticity	0	1 (<1)	0
Syncope	0	1 (<1)	4 (1)
Psychiatric Disorders	4 (1)	2 (1)	8 (2)
Affective Disorder	1 (<1)	0	1 (<1)
Alcohol Abuse	0	1 (<1)	0
Anxiety	0	1 (<1)	0
Bipolar I Disorder	1 (<1)	0	0
Completed Suicide	1 (<1)	1 (<1)	0
Depression	1 (<1)	1 (<1)	1 (<1)

	Control	Experimental	
	Arm 1† PR48 N=363	Arm 2†† RGT N=368	Arm 3††† BOC/PR48 N=366
Drug Abuse	0	0	1 (<1)
Drug Dependence	1 (<1)	0	0
Intentional Self-Injury	1 (<1)	0	0
Personality Disorder	1 (<1)	0	0
Psychiatric Decompensation	0	0	1 (<1)
Suicidal Ideation	1 (<1)	0	4 (1)
Suicide Attempt	1 (<1)	0	1 (<1)
Renal and Urinary Disorders	1 (<1)	0	0
Glomerulonephritis Minimal Lesion	1 (<1)	0	0
Renal Tubular Necrosis	1 (<1)	0	0
Reproductive System and Breast Disorders	0	0	1 (<1)
Scrotal Pain	0	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	1 (<1)	4 (1)	3 (1)
Cough	0	0	2 (1)
Dyspnoea	0	0	1 (<1)
Haemoptysis	0	1 (<1)	0
Pleural Fibrosis	0	1 (<1)	0
Pneumothorax	1 (<1)	0	0
Pulmonary Embolism	0	2 (1)	0
Skin and Subcutaneous Tissue Disorders	0	0	1 (<1)
Pruritus	0	0	1 (<1)
Rash Erythematous	0	0	1 (<1)
Social Circumstances	1 (<1)	0	1 (<1)
Alcohol Use	0	0	1 (<1)
Physical Assault	1 (<1)	0	0
Surgical and Medical Procedures	2 (1)	0	1 (<1)
Cholecystectomy	1 (<1)	0	0
Laryngeal Operation	0	0	1 (<1)
Skin Neoplasm Excision	1 (<1)	0	0
Vascular Disorders	0	1 (<1)	4 (1)
Accelerated Hypertension	0	0	1 (<1)
Arterial Thrombosis Limb	0	0	1 (<1)
Hypertensive Crisis	0	0	1 (<1)

	Control	Experimental	
	Arm 1[†] PR48 N=363	Arm 2[††] RGT N=368	Arm 3[†††] BOC/PR48 N=366
Hypotension	0	1 (<1)	1 (<1)

BOC=boceprevir 800 mg TID; PEG2b, P=peginterferon alfa-2b 1.5 µg/kg QW; QW=once weekly; RBV, R=ribavirin 600 to 1400 mg/day; RGT=response-guided therapy; TID=three times daily.

[§] Includes all serious clinical adverse events occurring on study treatment or within 30 days of its discontinuation, regardless of causality. Terms are from MedRA version 13.0, and listed by decreasing overall frequency.

[†]Arm 1 (PR48) = PEG2b + RBV for 48 weeks.

[††]Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (subjects with undetectable HCV-RNA at Treatment Week [TW] 8 and all subsequent assays through TW 24) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (subjects with detectable HCV-RNA at TW 8 or any subsequent assay up to TW 24).

[†††]Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Subject accounting and disposition

A CONSORT diagram shows patient disposition through end of follow-up at Week 72. A total of 2 randomized patients (both in Cohort 1) did not receive study drugs. SVR was determined 24 weeks following cessation of study therapy.

Figure S2A. Forest plots showing the odds ratios for sustained virologic response rates by baseline subgroups comparing each boceprevir arm (Arm 2 and Arm 3) to the control arm (Arm 1) in all treated patients in the combined cohorts

The odds ratios are derived from all treated patients in both cohorts. Odds ratios are presented on a logarithmic scale in Forest plots to provide an estimate of treatment effect in subpopulations at baseline. The solid vertical line at unity indicates no treatment difference (odds ratio=1). The dotted lines with arrowheads show that the values for "statin user" are off-scale (due to the very small numbers of patients in the study taking statins).

Figure S2B. Forest plot showing the odds ratios for the sustained virologic response rates comparing Arm 3 versus Arm 2 for combined subgroups from both cohorts

The odds ratios are derived from all treated patients in both cohorts. Odds ratios are presented on a logarithmic scale in Forest plots to provide an estimate of treatment effect in subpopulations at baseline. The solid vertical line at unity indicates no treatment difference (odds ratio=1).

Figure S1.

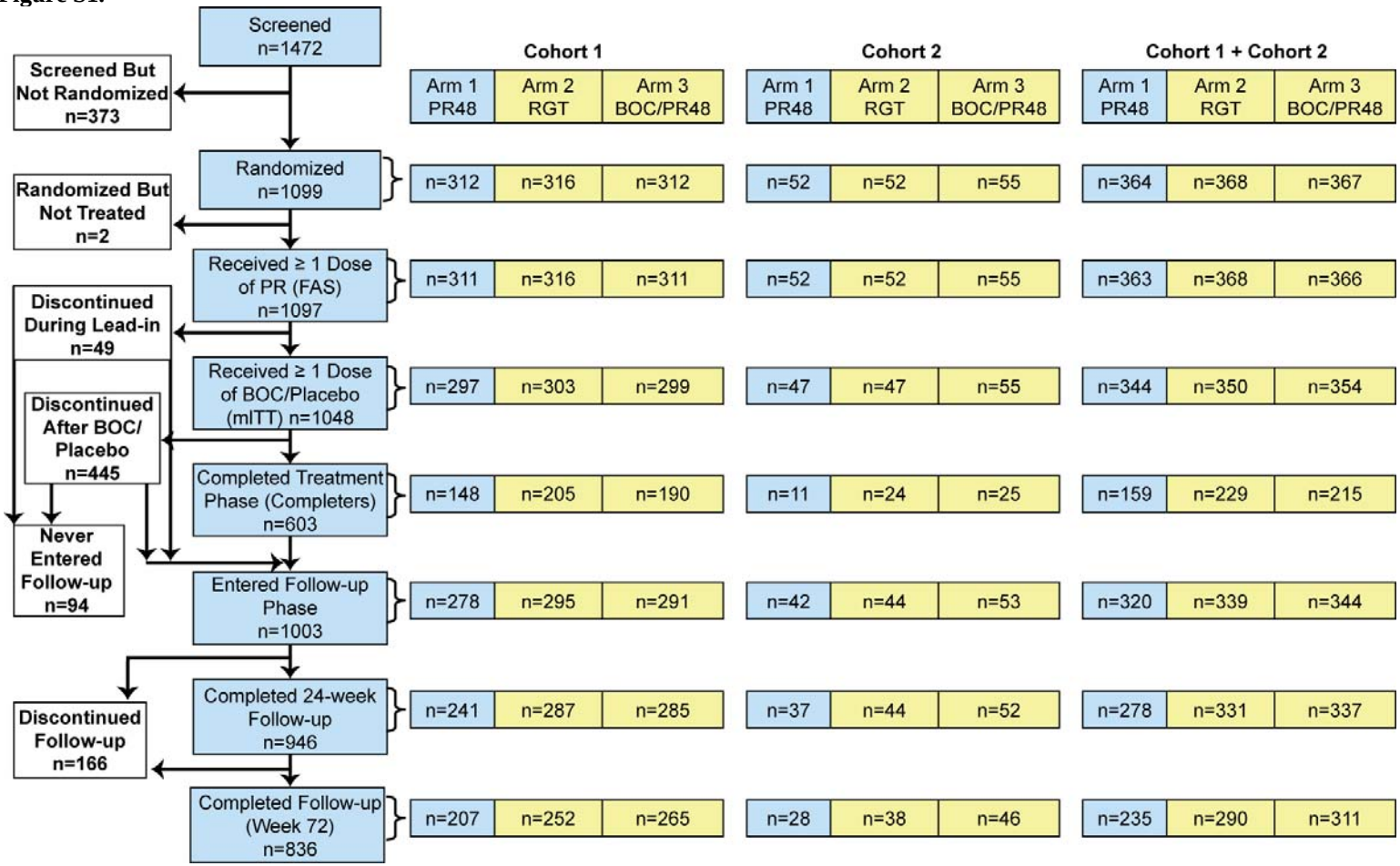
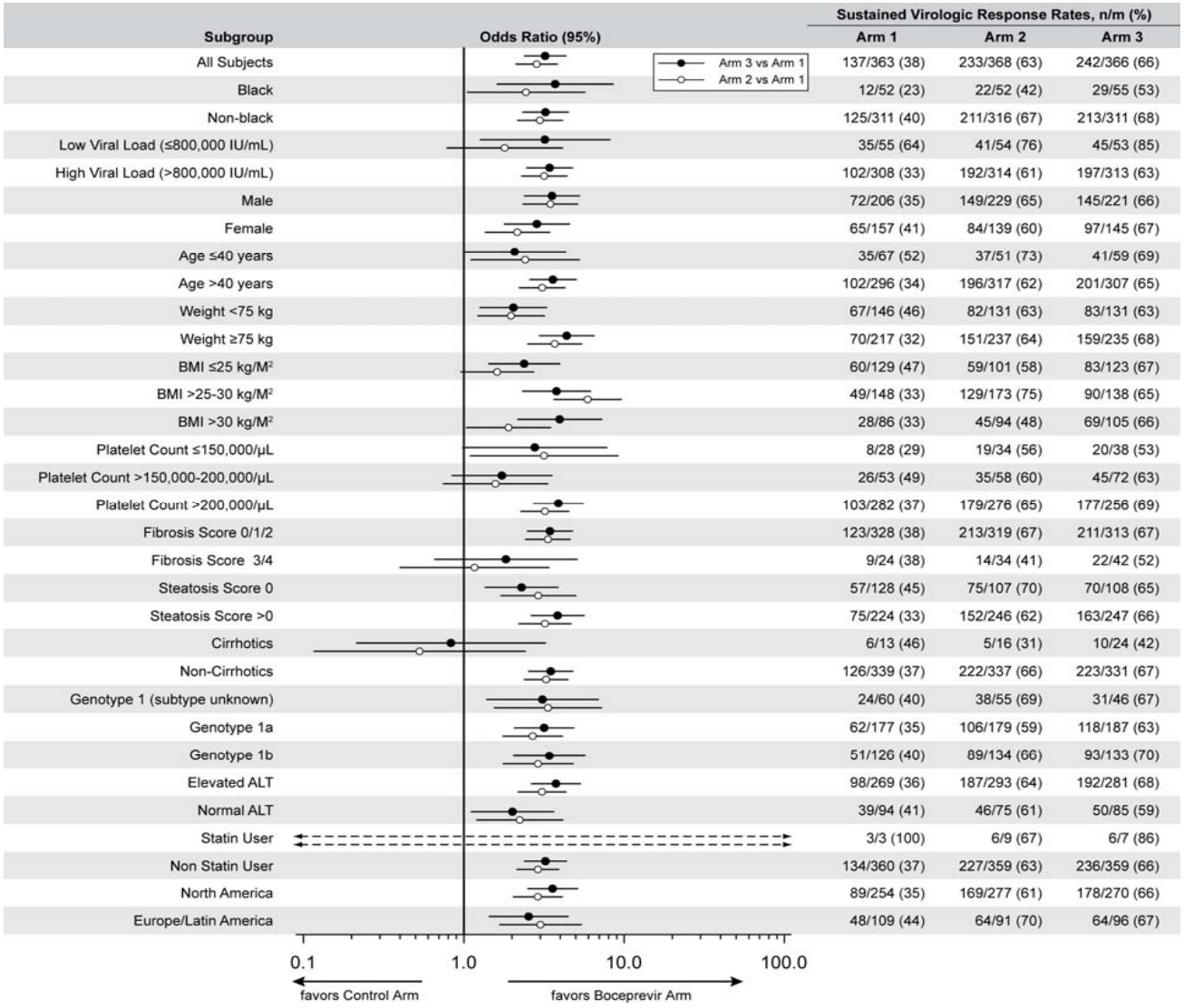
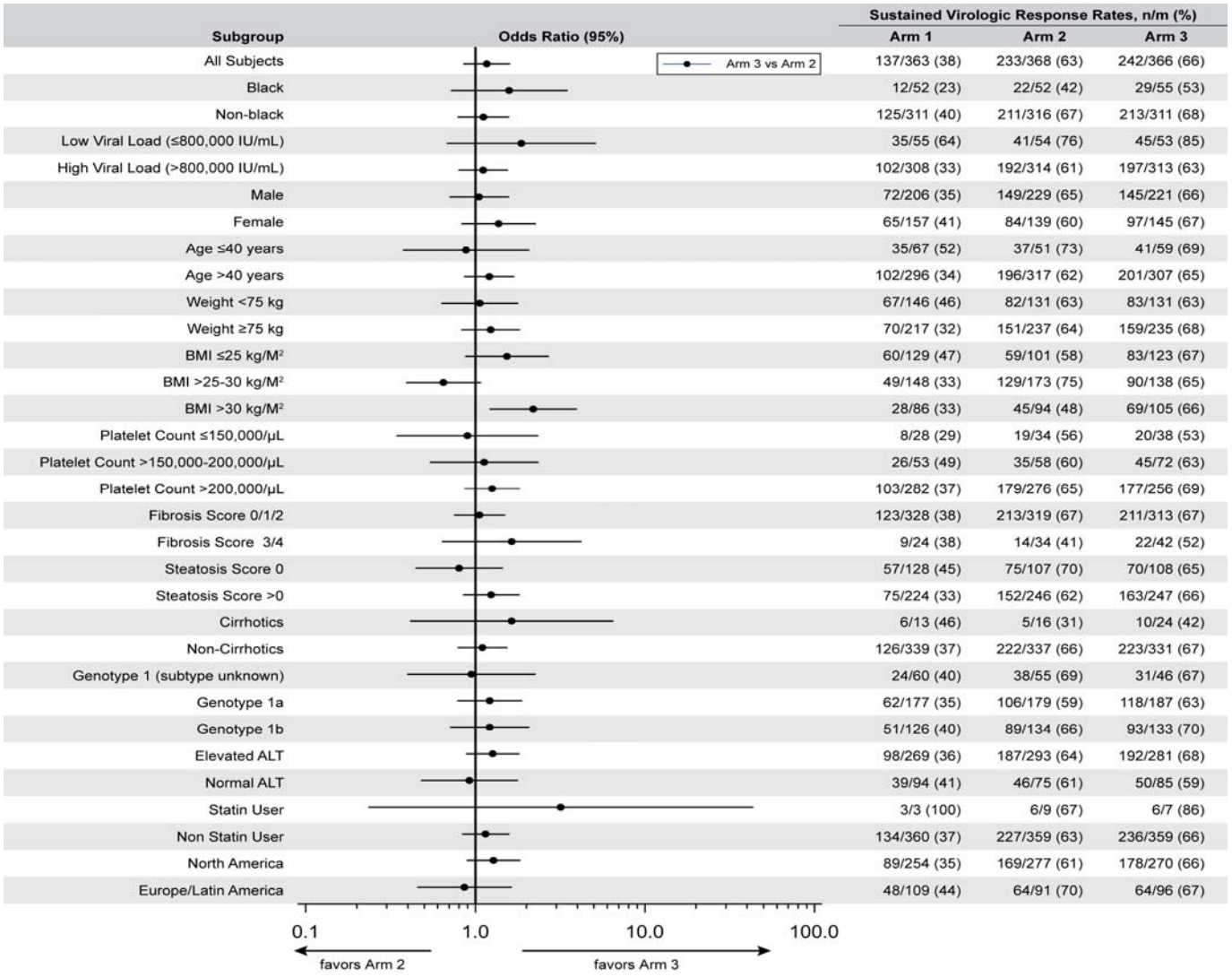

Screened
n=1472
Screened But Not Randomized n=373
Randomized
n=1099
Randomized But Not Treated n=2
Received ≥ 1 Dose of PR (FAS) n=1097
Discontinued During Lead-in n=49
Received ≥ 1 Dose of BOC/Placebo (mITT) n=1048
Discontinued After BOC/ Placebo n=445
Completed Treatment Phase (Completers) n=603
Never Entered Follow-up n=94
Entered Follow-up Phase n=1003
Completed 24-week Follow-up n=946
Discontinued Follow-up n=166
Completed Follow-up (Week 72) n=836
Cohort 1
Cohort 2
Cohort 1 + Cohort 2
Arm 1 PR48
Arm 2 RGT
Arm 3 BOC/PR48
n=312 n=316 n=312 n=52 n=52 n=55 n=364 n=368 n=367
n=311 n=316 n=311 n=52 n=52 n=55 n=363 n=368 n=366
n=297 n=303 n=299 n=47 n=47 n=55 n=344 n=350 n=354
n=148 n=205 n=190 n=11 n=24 n=25 n=159 n=229 n=215
n=278 n=295 n=291 n=42 n=44 n=53 n=320 n=339 n=344
n=241 n=287 n=285 n=37 n=44 n=52 n=278 n=331 n=337
n=207 n=252 n=265 n=28 n=38 n=46 n=235 n=290 n=311

Figure S2A. Boceprevir Arms 2 and 3 versus Control Arm 1



Subgroup	Sustained Virologic Response Rates, n/m (%)		
	Arm 1	Arm 2	Arm 3
All Subjects	137/363 (38)	233/368 (63)	242/366 (66)
Black	12/52 (23)	22/52 (42)	29/55 (53)
Non-black	125/311 (40)	211/316 (67)	213/311 (68)
Low Viral Load (≤800,000 IU/mL)	35/55 (64)	41/54 (76)	45/53 (85)
High Viral Load (>800,000 IU/mL)	102/308 (33)	192/314 (61)	197/313 (63)
Male	72/206 (35)	149/229 (65)	145/221 (66)
Female	65/157 (41)	84/139 (60)	97/145 (67)
Age ≤40 years	35/67 (52)	37/51 (73)	41/59 (69)
Age >40 years	102/296 (34)	196/317 (62)	201/307 (65)
Weight <75 kg	67/146 (46)	82/131 (63)	83/131 (63)
Weight ≥75 kg	70/217 (32)	151/237 (64)	159/235 (68)
BMI ≤25 kg/M^2	60/129 (47)	59/101 (58)	83/123 (67)
BMI >25-30 kg/M^2	49/148 (33)	129/173 (75)	90/138 (65)
BMI >30 kg/M^2	28/86 (33)	45/94 (48)	69/105 (66)
Platelet Count ≤150,000/µL	8/28 (29)	19/34 (56)	20/38 (53)
Platelet Count >150,000-200,000/µL	26/53 (49)	35/58 (60)	45/72 (63)
Platelet Count >200,000/µL	103/282 (37)	179/276 (65)	177/256 (69)
Fibrosis Score 0/1/2	123/328 (38)	213/319 (67)	211/313 (67)
Fibrosis Score 3/4	9/24 (38)	14/34 (41)	22/42 (52)
Steatosis Score 0	57/128 (45)	75/107 (70)	70/108 (65)
Steatosis Score >0	75/224 (33)	152/246 (62)	163/247 (66)
Cirrhotics	6/13 (46)	5/16 (31)	10/24 (42)
Non-Cirrhotics	126/339 (37)	222/337 (66)	223/331 (67)
Genotype 1 (subtype unknown)	24/60 (40)	38/55 (69)	31/46 (67)
Genotype 1a	62/177 (35)	106/179 (59)	118/187 (63)
Genotype 1b	51/126 (40)	89/134 (66)	93/133 (70)
Elevated ALT	98/269 (36)	187/293 (64)	192/281 (68)
Normal ALT	39/94 (41)	46/75 (61)	50/85 (59)
Statin User	3/3 (100)	6/9 (67)	6/7 (86)
Non Statin User	134/360 (37)	227/359 (63)	236/359 (66)
North America	89/254 (35)	169/277 (61)	178/270 (66)
Europe/Latin America	48/109 (44)	64/91 (70)	64/96 (67)

Figure S2B. Arm 3 versus Arm 2



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